Prostate Cancer Prevention Trial (PCPT)

Oncologic Drugs Advisory Committee Meeting
December 1, 2010

Southwest Oncology Group (SWOG)
Merck

Agenda

- Vivian L. Fuh, MD — Merck
  - Introduction, Regulatory History
- Ian M. Thompson, Jr., M.D. — SWOG
  - Prostate Cancer Prevention Trial
- Vivian L. Fuh, MD — Merck
  - Labeling Proposal

Attendees

SWOG

- Ian M. Thompson, Jr., M.D.
- Catherine Tangen, Dr.P.H.
- Phyllis Goodman, M.S.
- Scott Lucia, M.D.

Consultant

- Janet Wittes, Ph.D.

PCPT: Regulatory History

- 1993: Landmark study initiated
  - Sponsored by NCI, conducted by SWOG
  - Primary hypothesis: finasteride 5 mg (PROSCAR®), type 2 5α-reductase inhibitor, reduces risk of prostate cancer
- 2003: Primary hypothesis met, study unblinded
  - Reduction in prevalence of prostate cancer overall
  - Unexpected increase in high-grade prostate cancer
  - Merck filed labeling supplement to add high-grade findings to PROSCAR label (ADVERSE REACTIONS)
- 2004: Merck received PCPT dataset from SWOG
  - Analyses conducted to evaluate high-grade disease findings supported hypothesis that findings may be explained by detection bias

PCPT: Regulatory History

- 2005: Merck filed 2nd PCPT labeling supplement
  - Revised labeling to add:
    - Primary study outcome
    - Detection bias may explain high-grade findings
  - Did not request indication for prostate cancer prevention
  - Consistent proposal filed worldwide
  - FDA not supportive of Merck's labeling proposal
    - Analyses of high-grade findings 'hypothesis-generating' and 'do not rise to the level of the label'
    - Inclusion of primary study outcome was 'an implied claim'
  - Based on clarity of FDA's position, Merck withdrew the U.S. labeling supplement for PCPT

PCPT: Regulatory History

- 2005-present: Multiple additional analyses of PCPT published
  - Consistent with earlier hypothesis of detection bias
  - Expanded understanding of sources of potential bias
- 2009: ASCO/AUA guideline on use of 5α-reductase inhibitors for prostate cancer chemoprevention
  - Recommended consideration of both benefits and risks for men concerned with their risk of prostate cancer

PCPT: Regulatory History

- 2009: FDA expressed intent to discuss PCPT with ODAC
  - To support discussions at ODAC, FDA requested Merck to file a supplemental NDA with accompanying labeling
- Merck responded by filing a labeling supplement in October 2009

PCPT: Labeling Proposal

- A more complete summary of results of PCPT in PROSCAR® labeling allows for better informed decisions by physicians and patients when considering use of PROSCAR as indicated for treatment of symptomatic BPH
- Merck filed the labeling supplement to add
  - Primary study outcome
  - Detection bias may explain high-grade findings
  - Reference to ASCO/AUA guideline
  - Clarification that this information is provided for consideration by physicians when treating men, or evaluating men for treatment, with PROSCAR for BPH
- Did not request indication for prostate cancer prevention

Agenda

- Vivian L. Fuh, MD — Merck
  - Introduction
- Ian M. Thompson, Jr., M.D. — SWOG
  - Prostate Cancer Prevention Trial
- Vivian L. Fuh, MD — Merck
  - Labeling Proposal

Prostate Cancer Prevention Trial

Ian M. Thompson, Jr., MD
PCPT Principal Clinical Investigator
Professor and Chair, Department of Urology
Executive Director, Cancer Therapy and Research Center
University of Texas Health Science Center
San Antonio, TX

What We Will Show

- Finasteride significantly reduces a man's risk of prostate cancer
- Increase in high-grade tumors observed with finasteride is likely to be an artifact due to improved detection
- Safety of finasteride consistent with established profile
  - Increase in sexual and breast-related side effects
  - Decrease in BPH symptoms and complications

Prostate Cancer Prevention Trial (PCPT)

- Funded by National Cancer Institute – Division of Cancer Prevention
- Designed and coordinated by Southwest Oncology Group (SWOG), initiated 1993
- Finasteride 5 mg vs. matching placebo
  - Study drug provided by Merck
- Randomized, double-blind, 7-year treatment
- 18,882 men from 218 study sites in U.S. and 1 in Canada
- Overseen by independent Data and Safety Monitoring Committee (DSMC)

Prostate Cancer

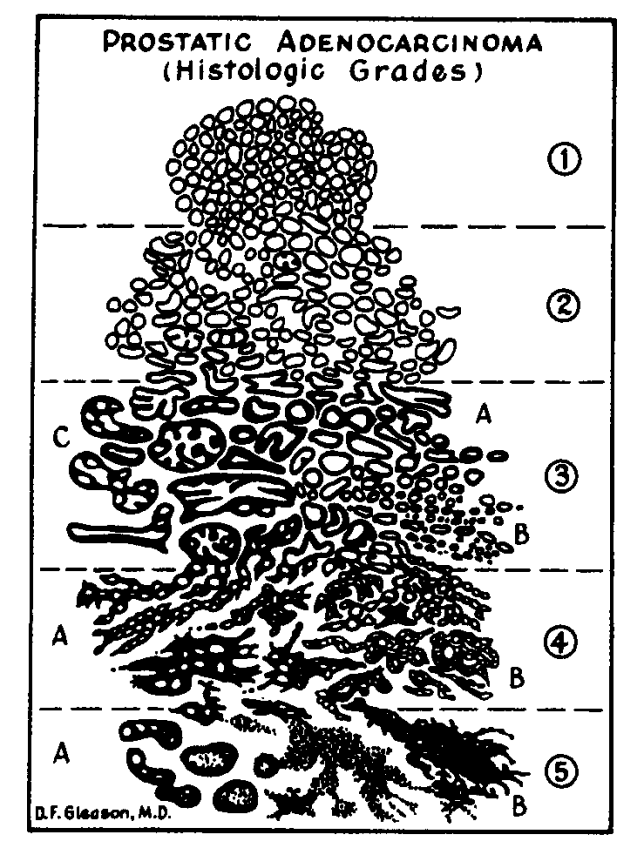
- Prostate cancer will be diagnosed in 217,730 men and cause 32,050 deaths in the U.S. in 2010
- Prostate cancer will represent 28% of cancer diagnoses and 11% of cancer deaths among U.S. men
- Lifetime risk of diagnosis is 15.7%; about 1 man in 6 will be diagnosed with prostate cancer
- Incidence predicted to increase with aging of the population and continued use of cancer screening

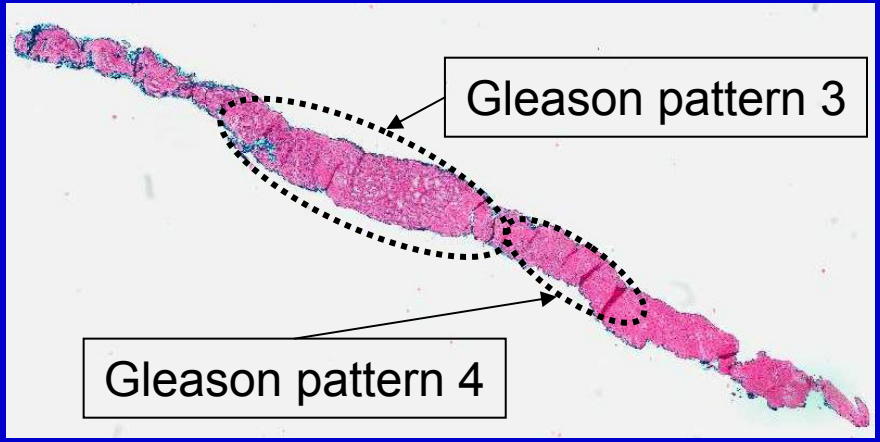
Jemal, et al. Cancer Statistics, 2010. CA Cancer J Clin 2010;60.

Prostate Cancer Diagnosis

- Majority of tumors detected by prostate-specific antigen (PSA) screening
- Elevated PSA or abnormal digital rectal examination (DRE) prompts ultrasound-guided prostate biopsy with multiple cores obtained
- Screening controversial but remains common in U.S.
  - U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial randomized screening study found no difference in mortality
  - European Randomized Study of Screening for Prostate Cancer (ERSPC) found 20% reduction in prostate cancer death with screening
- Currently, ~50% of men over age 50 have annual PSA testing

Prostate Cancer Grading





Resultant Gleason score =
(greatest volume) + (second greatest volume*)

In this case, Gleason score = 3+4 = 7

(*or highest grade)

Gleason, DF. The Veterans Administration Cooperative Urological Research Group. Histologic grading and clinical staging of prostatic carcinoma. Tannenbaum M (ed). Urologic Pathology: The Prostate. Lea & Febiger, Philadelphia, 1977: pp. 171-197 (by permission of Lippincott Williams & Wilkins).

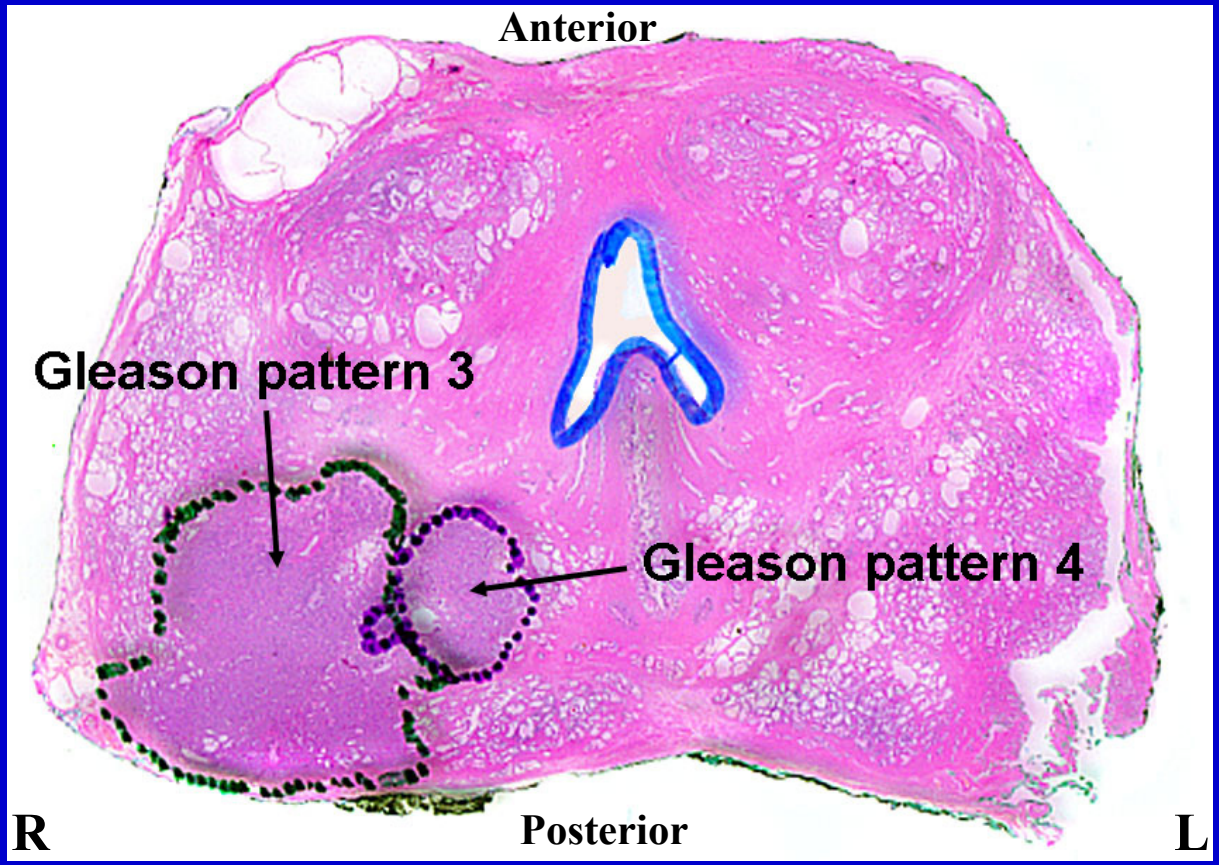
Prostate Cancer Grading and Treatment

- Most common prostate cancer Gleason score = 3+3 = 6
- Although cure rates very high with surgery or radiation, untreated Gleason 3+3 disease historically associated with 20-year cancer-specific mortality rates of 20-30%[1]
- As a result, over 90% of these prostate cancers are treated with surgery or radiation in the U.S.[2]

[1]Albertsen PC, et al. JAMA 2005;293:2095-2101. [2]Cooperberg MR, et al. J Clin Onc 2010;28:1117-23.

Undergrading of Cancer at Biopsy

Approximately 20-30% of all cancers diagnosed from biopsy are upgraded to higher Gleason score (when prostatectomy specimen examined)



Smaldone MC, et al. J Urology 2010;183:138-43.

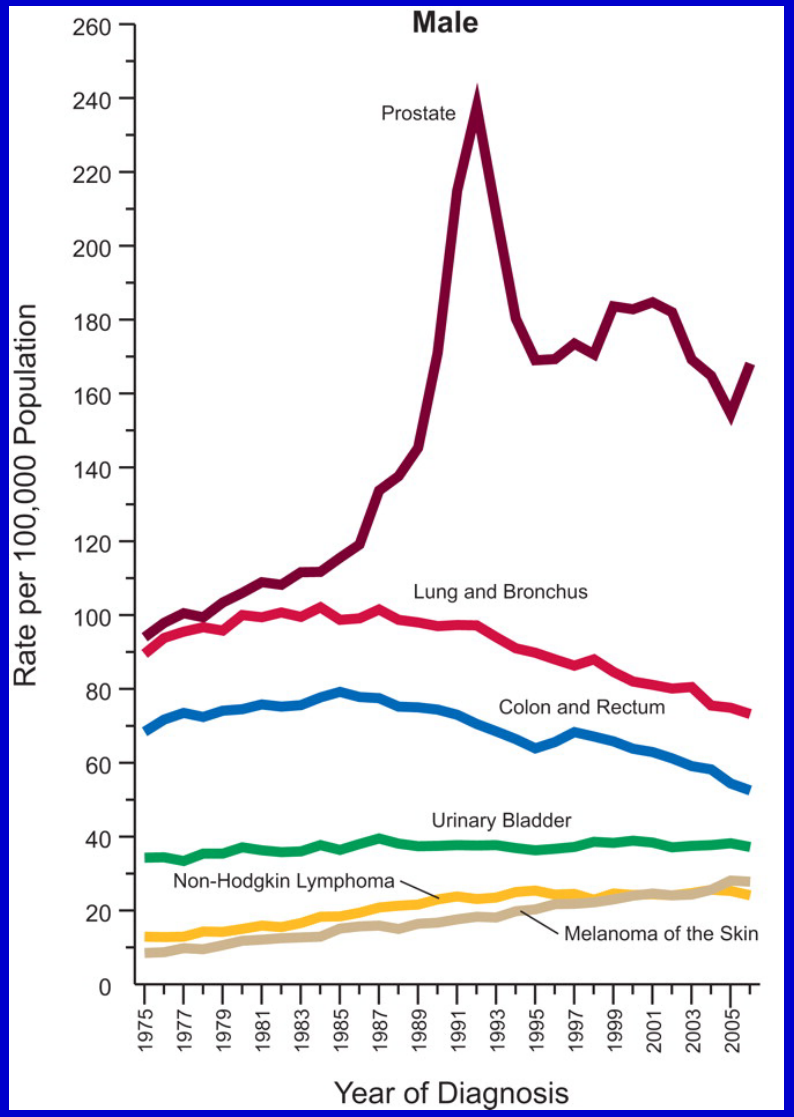
Prostate Cancer Treatment

- Treatment options: surgery, radiation, hormonal therapy, surveillance
- Over 90% of men with localized cancer are treated
  - Surgery/radiation: poor erections (51-60%)†, incontinence requiring pads (3-20%)†, gastrointestinal bleeding, pain, urethral stricture
  - Hormones: sexual dysfunction, insulin resistance, cardiovascular disease
  - 16-34% of men will experience cancer recurrence
- Surveillance: cancer progression, risk of bleeding or infection with repeated biopsies, anxiety
- Regardless of treatment selected, diagnosis of any prostate cancer has a profoundly adverse impact on a man's life

† 2 years after treatment.

Background of PCPT

- Late 1980s – dramatic increase in prostate cancer diagnosis
- Most likely due to PSA testing

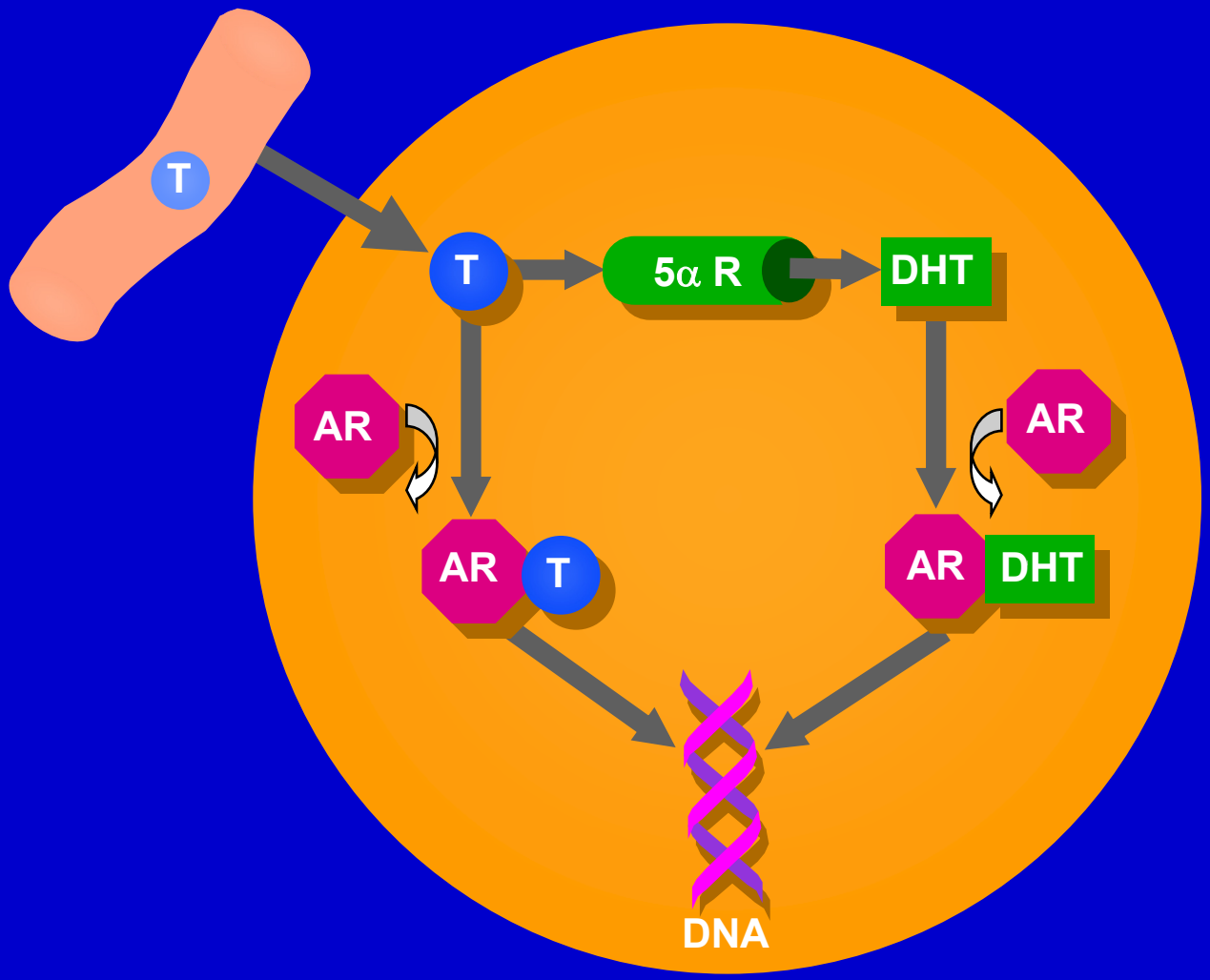


Jemal, et al. Cancer Statistics. 2010.
CA Cancer J Clin. 2010;60.

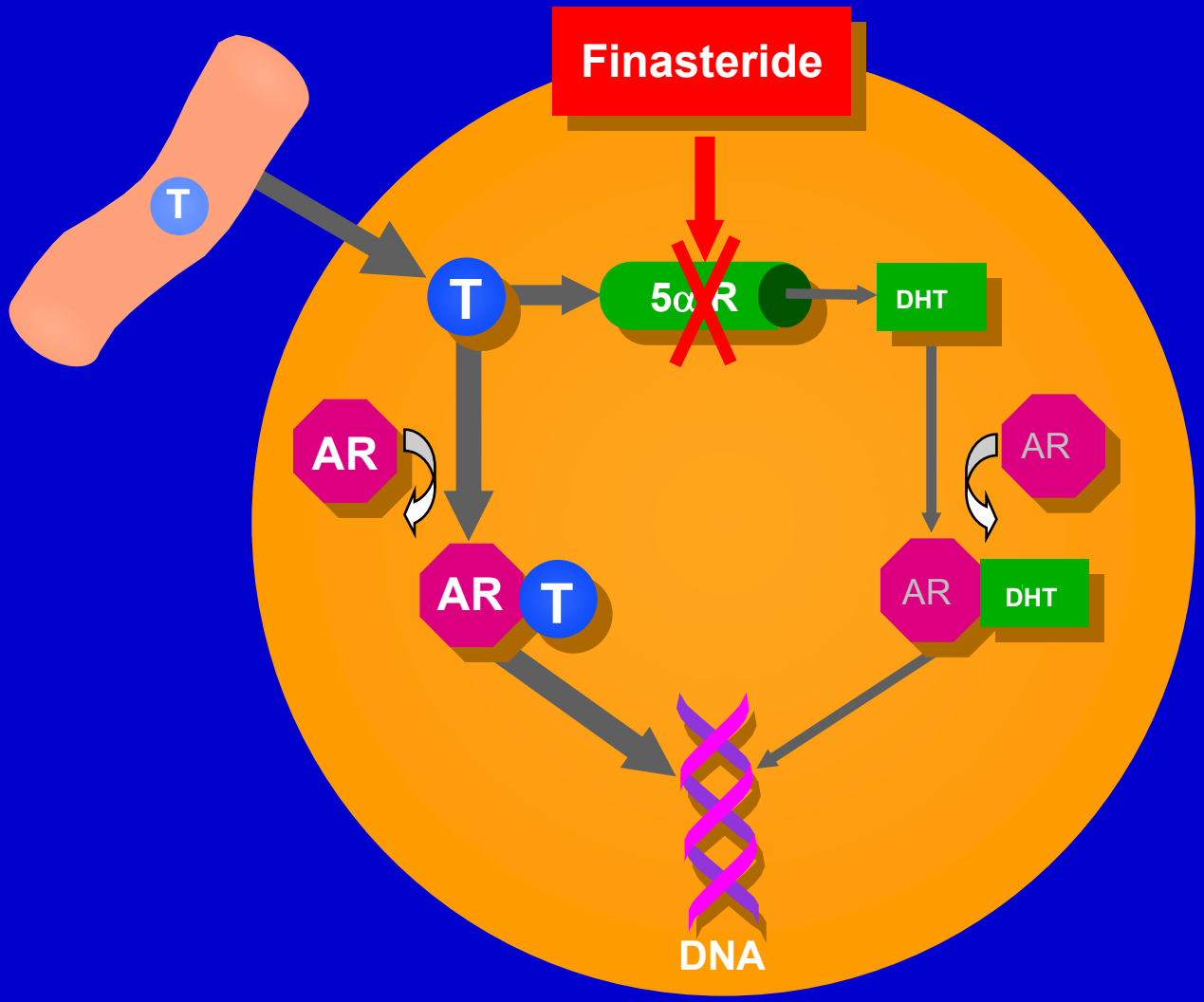
Background of PCPT

- Public health concern regarding increase in prostate cancer diagnoses
- Relationship between androgens and prostate cancer long acknowledged
- 1992: finasteride 5 mg (PROSCAR®), type 2 5α-reductase inhibitor, first agent in class available for treatment of BPH
  - Significantly reduces the intra-prostatic androgen, dihydrotestosterone (DHT)
- Unique opportunity to test the hypothesis that lowering intra-prostatic DHT reduces the risk of prostate cancer

Androgens in the Prostate



Androgens in the Prostate



PCPT Design
Primary Endpoint Options Considered

- Survival endpoint
  - Not feasible due to size, cost, contamination
- Cancer endpoint, no diagnostic intervention during treatment
  - At study end perform prostate biopsy in all subjects
  - Inconsistent with clinical practice, ethical considerations
- Cancer endpoint, diagnostic intervention during treatment
  - At study end perform prostate biopsy on those without cancer
  - Feasible, acceptable to patients
  - *Clinically important endpoint*

PCPT Design
Controlling Detection Bias

- Endpoint selected: cancer prevalence
  - PSA and DRE screening, biopsy prompts
  - At study end, end-of-study (EOS) biopsy
  - Period prevalence = total prostate cancers diagnosed
- Intervention (finasteride) affects prostate cancer detection
  - Finasteride lowers PSA by ~50% in men with BPH
    - Significant bias without adjustment
    - PSA multiplied by 2.0 in men using finasteride for BPH
  - In PCPT, adjustment of PSA in finasteride group
    - Initially PSA multiplied by 2.0 based on data in men with BPH
    - Targeted adjustment for similar biopsy rate between groups
    - Beginning at participant's 4th year, PSA multiplied by 2.3

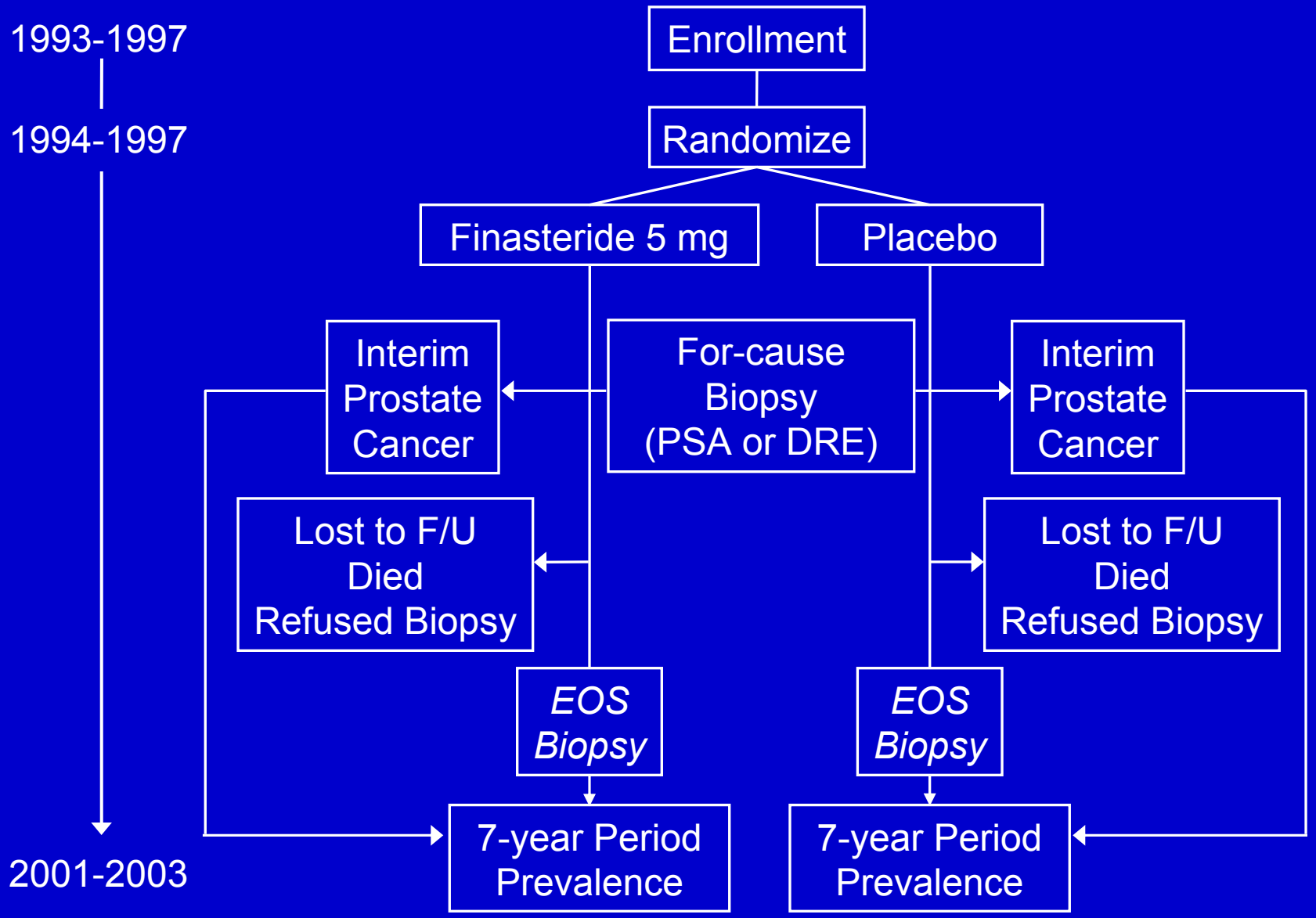
Primary Endpoint Options

- Period prevalence: prespecified primary endpoint
  - Histologically-proven presence or absence of prostate cancer over 7 years (known prostate cancer status at 7 years)
  - Absence of prostate cancer defined as negative EOS biopsy at Year 7
- Clinical incidence (excluding EOS biopsy data) considered but not selected:
  - Diagnosis dependent only on “for-cause” biopsies prompted by elevated PSA or abnormal DRE
  - PSA, DRE, and potentially other factors suspected at outset (and subsequently shown) as sources of bias, predicted in original study design

PCPT Design: Study Population

- Decision made to study broad, low-moderate risk population
  - Most generalizable
  - Allows conclusions regarding higher risk subgroups
- Eligibility criteria
  - 55 years of age or older
  - Overall good health
  - DRE not suspicious for prostate cancer
  - PSA ≤3.0 ng/mL (measured by a Central Laboratory)
  - American Urological Association (AUA) Symptom Score <20
    - Included men with AUA symptom scores (8 to 19), consistent with moderate obstructive symptoms of BPH

PCPT Schema



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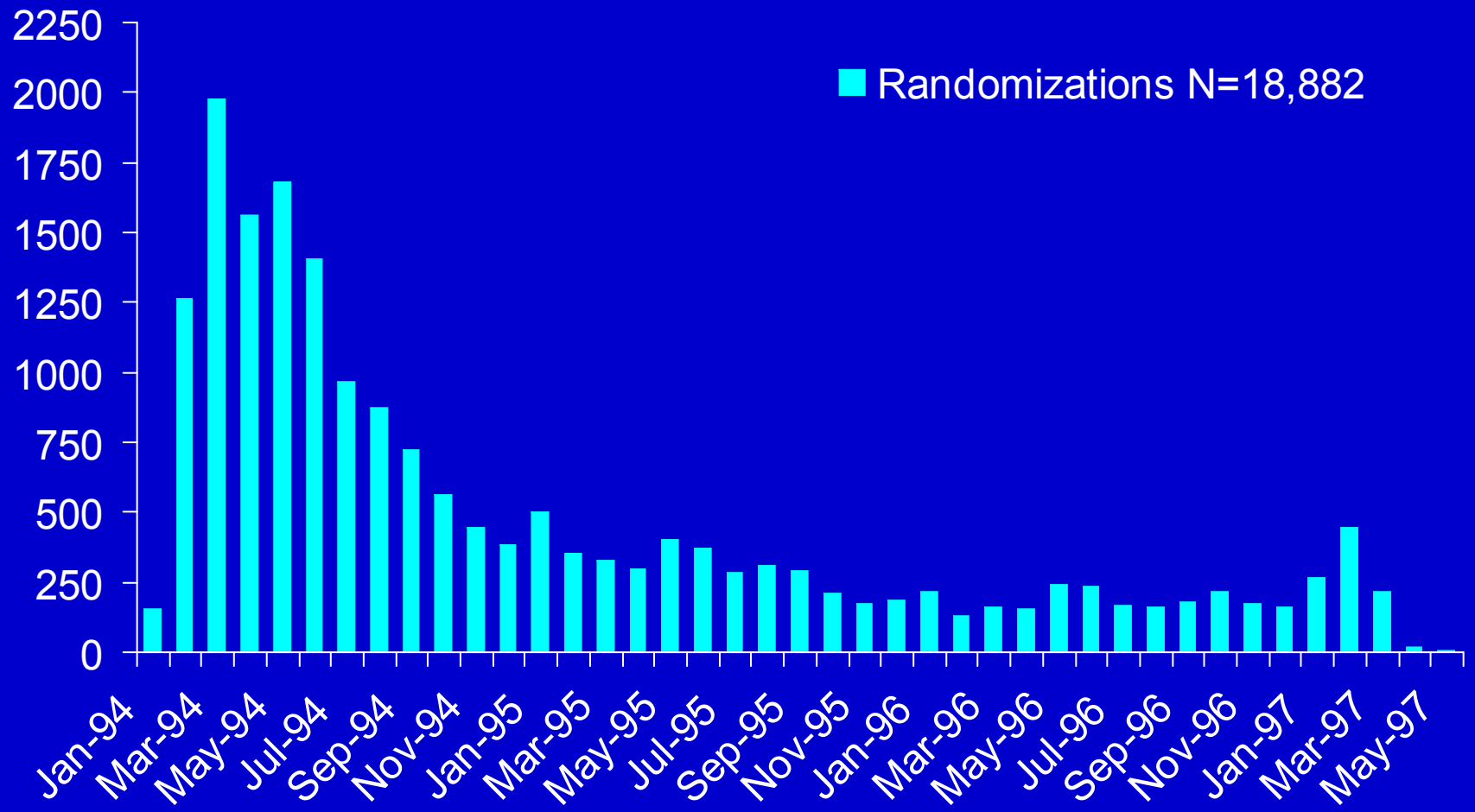
Categorization of Cancers in PCPT

- For-cause
  - Biopsies for PSA >4.0 ng/mL or abnormal DRE
    - Common PSA threshold used clinically at outset of PCPT
  - Any prostate cancer diagnosis made in usual clinical practice
- End-of-study
  - Year 7 biopsies with PSA ≤4.0 ng/mL and normal DRE
  - EOS biopsies *critical* to establish whether cancer present
    - Necessary to reduce impact of potential bias in cancer detection due to known actions of finasteride
    - Clinically significant cancers occur with PSA ≤4.0 ng/mL and normal DRE

Follow-Up

- Clinic visit every 6 months
  - Assessed for side effects, medical events
  - Previous study drug returned for assessment of adherence
  - Study drug dispensed
- Annual visit
  - Limited physical exam
  - DRE, PSA
  - Biopsy recommended if abnormal DRE elevated PSA (>4.0 ng/mL)
    - PSA adjusted for effect of finasteride
- Telephone calls at months 3 and 9 annually
- Blinded central pathology review

Participant Accrual
January 1994 - May 1997



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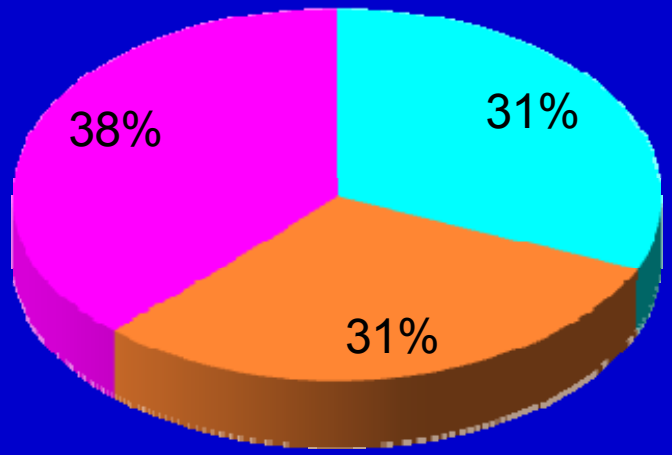
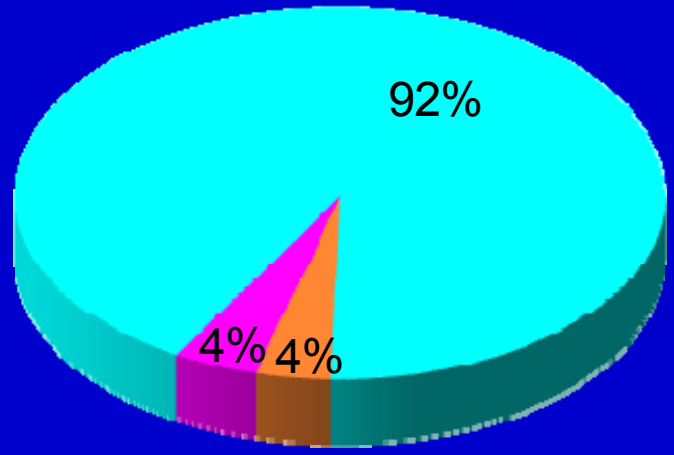
Baseline Characteristics

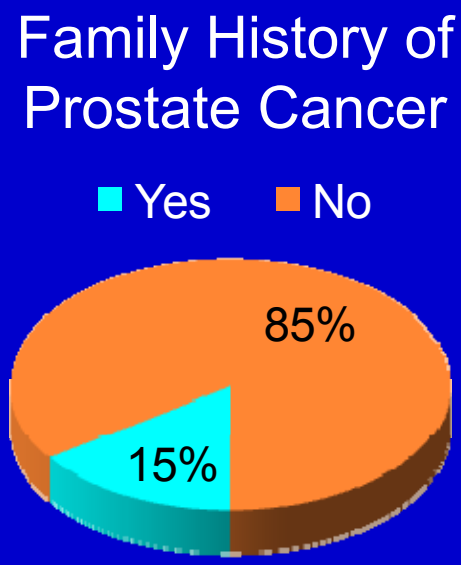
Age

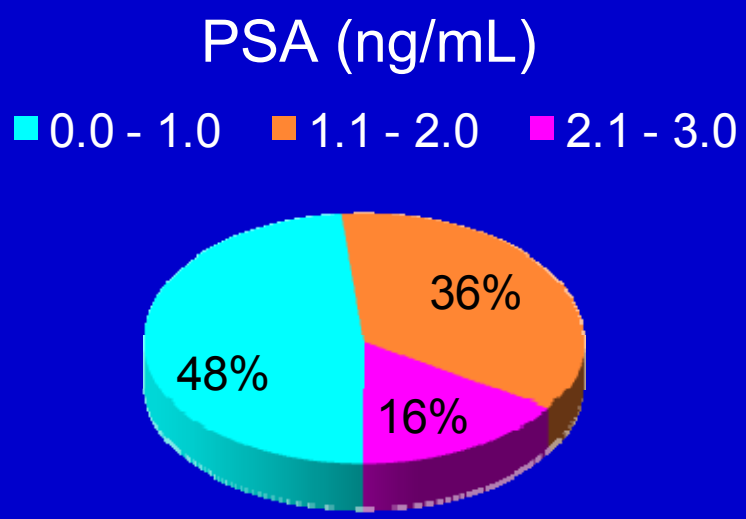


Race



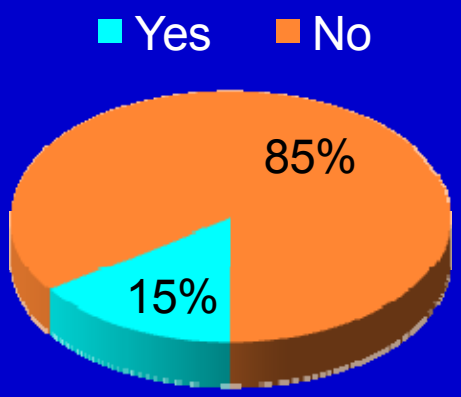
Baseline Characteristics



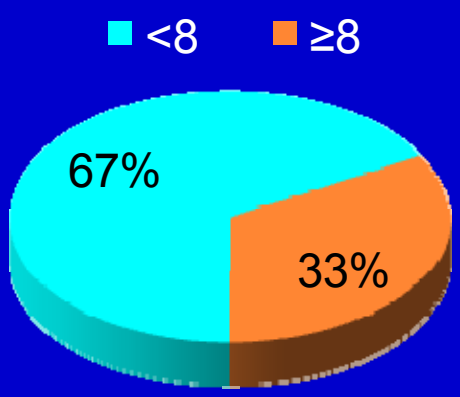


Baseline Characteristics

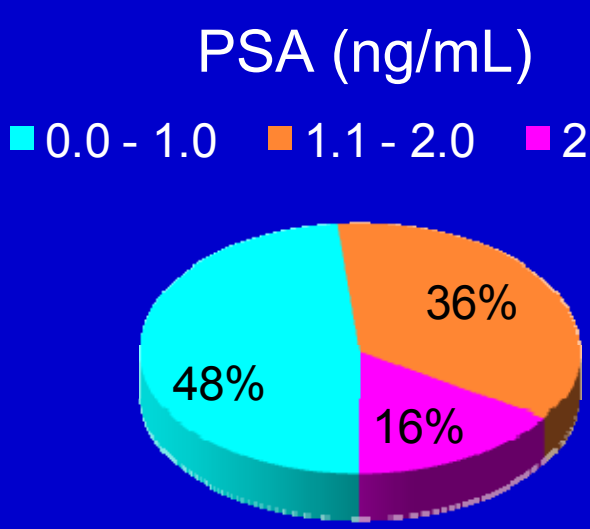
Family History of Prostate Cancer



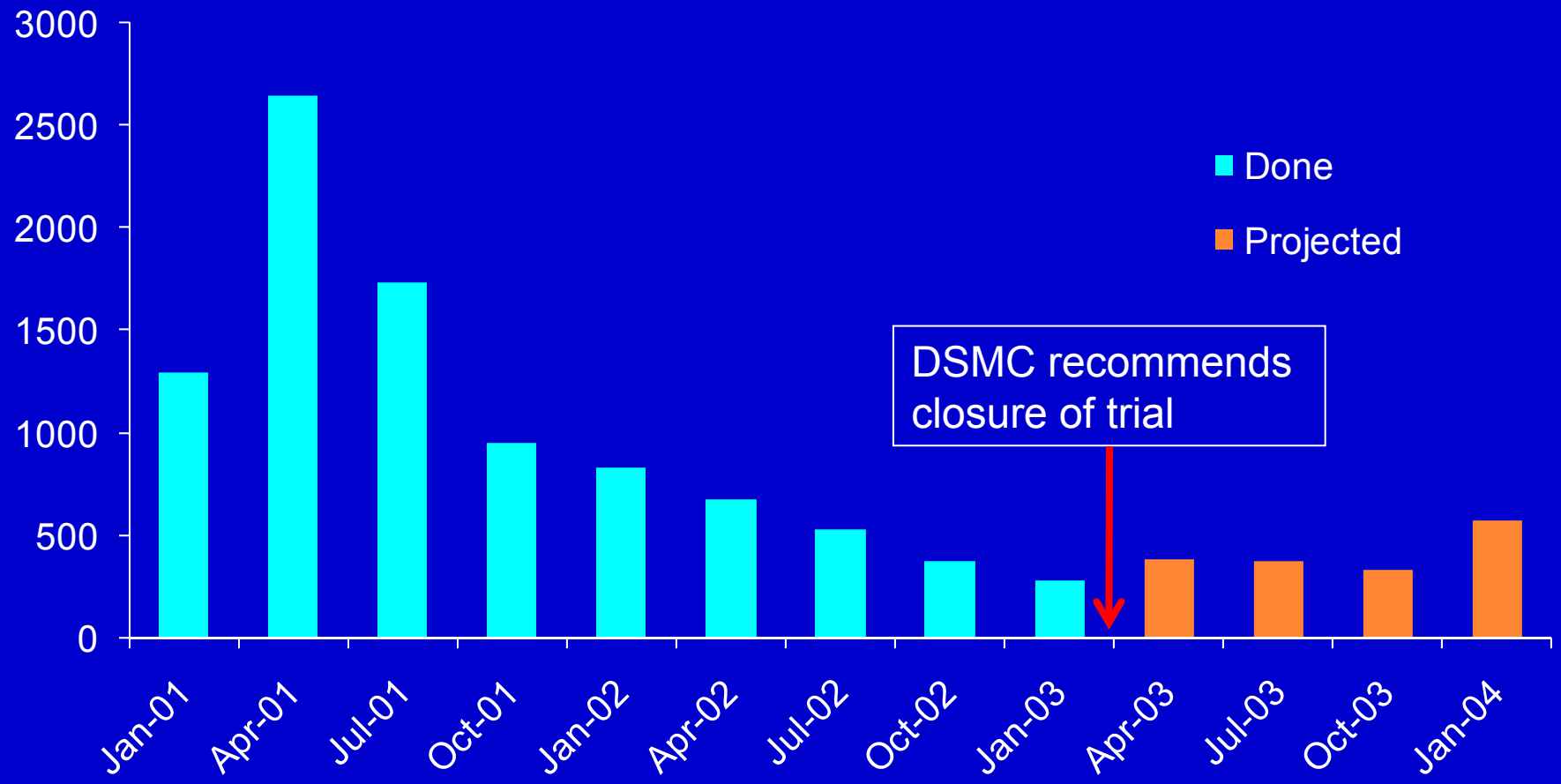
AUA Symptom Score



PSA (ng/mL)



End-of-Study Biopsies



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Study Close-Out Timeline

- February 21, 2003: DSMC recommends study closure
- March 19, 2003: NEJM dataset cutoff date
- June 23, 2003: Trial unblinding (investigators notified)
- June 24, 2003: Online publication in NEJM
- July 17, 2003: Print publication in NEJM
- December 31, 2003: Final study prostate biopsy performed
- **January 15, 2004: Dataset cutoff date for primary efficacy and safety analyses presented today**

SWOG Prespecified Primary Analysis

- Men with endpoint determination within 7 years + 90 days of randomization
  - Prostate cancer diagnosed prior to EOS biopsy
  - EOS biopsy either negative or positive for prostate cancer
  - Excluded prostate cancers diagnosed after 7 years + 90 days
- Finasteride (n=4775), placebo (n=5123)
- *Estimate of treatment effect better reflects true impact of finasteride on cancer prevention as only men with an endpoint determination included in analysis*

Modified Intention-to-Treat (MITT) Prespecified Secondary Analysis

- All randomized eligible men (N=18,880)
  - Excluded 2 men with prior prostate cancer diagnosis
- All prostate cancers detected
- Men without EOS biopsy assumed not to have prostate cancer
- Finasteride (n=9423), placebo (n=9457)
- *Preserves randomization for between-group comparisons but underestimates period prevalence of prostate cancer in both treatment groups*

Rejected Analysis

- Analyze only cancers diagnosed from for-cause biopsies
- Clinically intuitive, however:
  - It was known that finasteride affects the prostate
    - Both PSA and prostate volume are reduced
  - It was uncertain how well PSA adjustment would work and whether performance of PSA would be affected
  - It was unknown whether performance of DRE and prostate biopsy would be impacted by change in prostate volume and no known way to control for a potential bias
- *Analysis rejected a priori because we could not ensure that prostate cancer detection would be equivalent in both treatment groups*

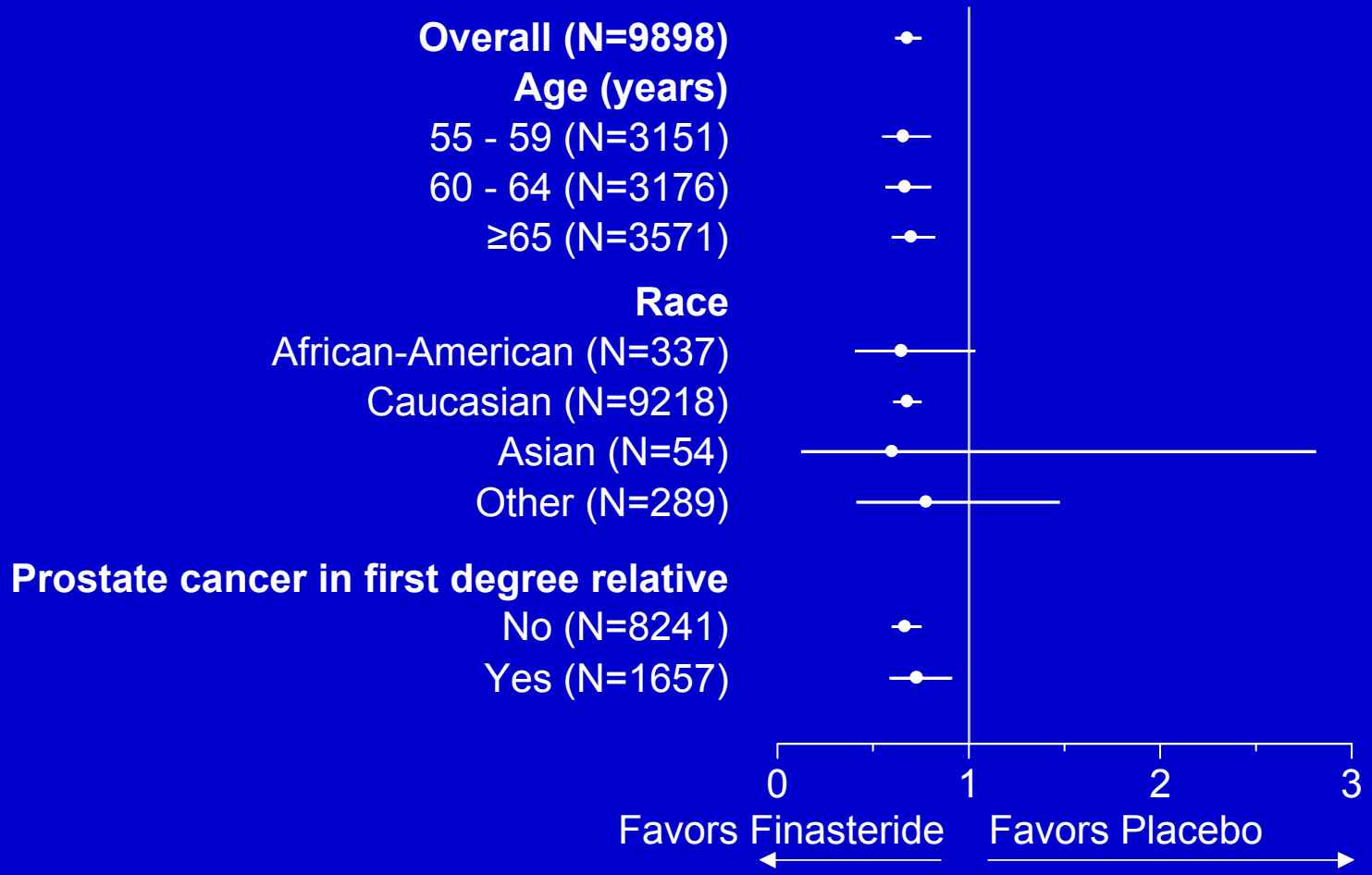
Significant Prostate Cancer Risk Reduction

	Finasteride	Placebo
SWOG		
Number evaluated	4775	5123
Number (%) with cancer	879 (18.4%)	1274 (24.9%)
Relative risk reduction	26.0%****	
Absolute risk reduction	6.5%	
MITT		
Number evaluated	9423	9457
Number (%) with cancer	979 (10.4%)	1407 (14.9%)
Relative risk reduction	30.2%****	
Absolute risk reduction	4.5%	

**** p<0.0001.

Odds Ratio for Prostate Cancer Consistent Across Subgroups SWOG Population

Age, Race and Family History



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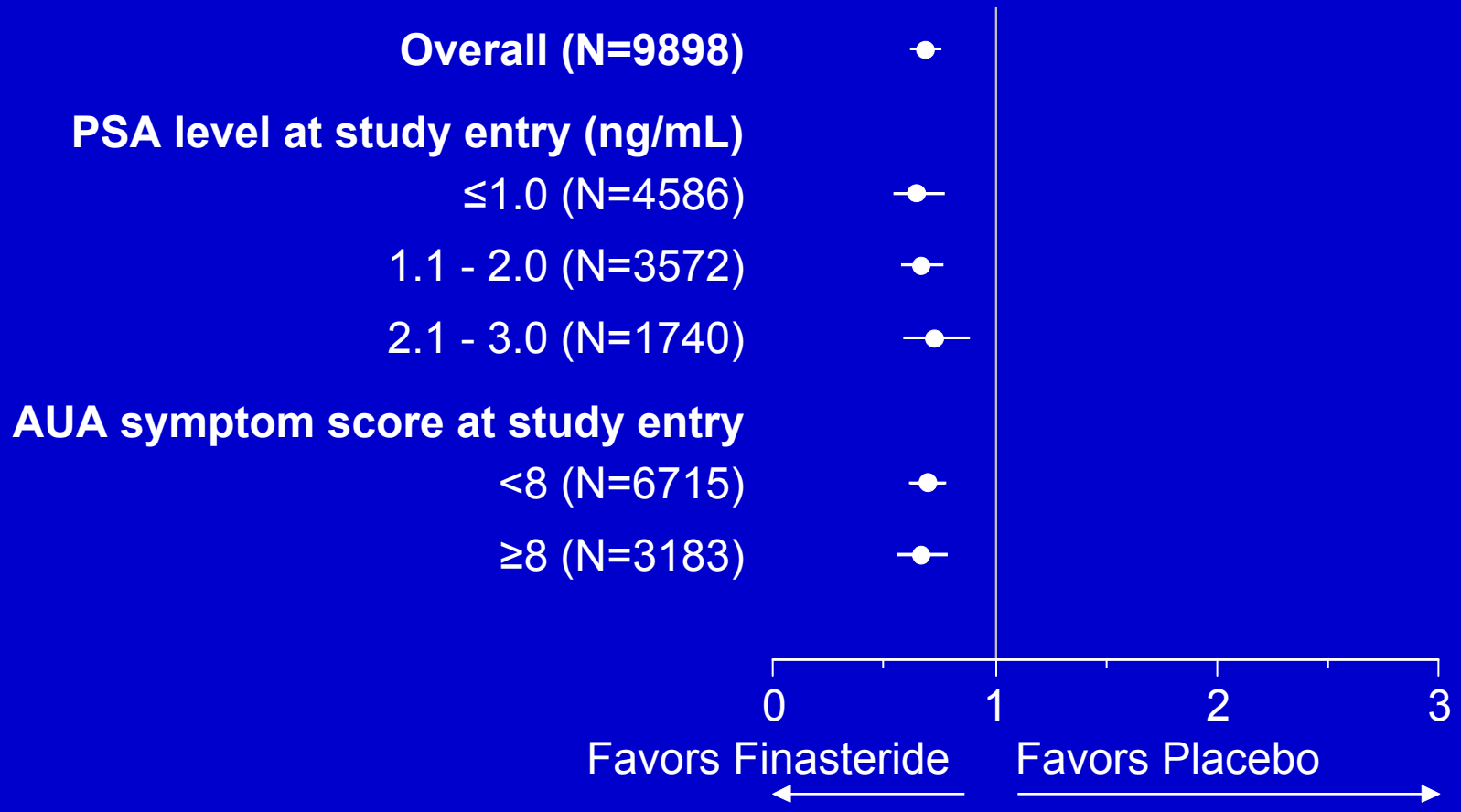
Odds Ratio for Prostate Cancer Consistent Across Subgroups SWOG Population

PSA and AUA Symptom Score at Study Entry



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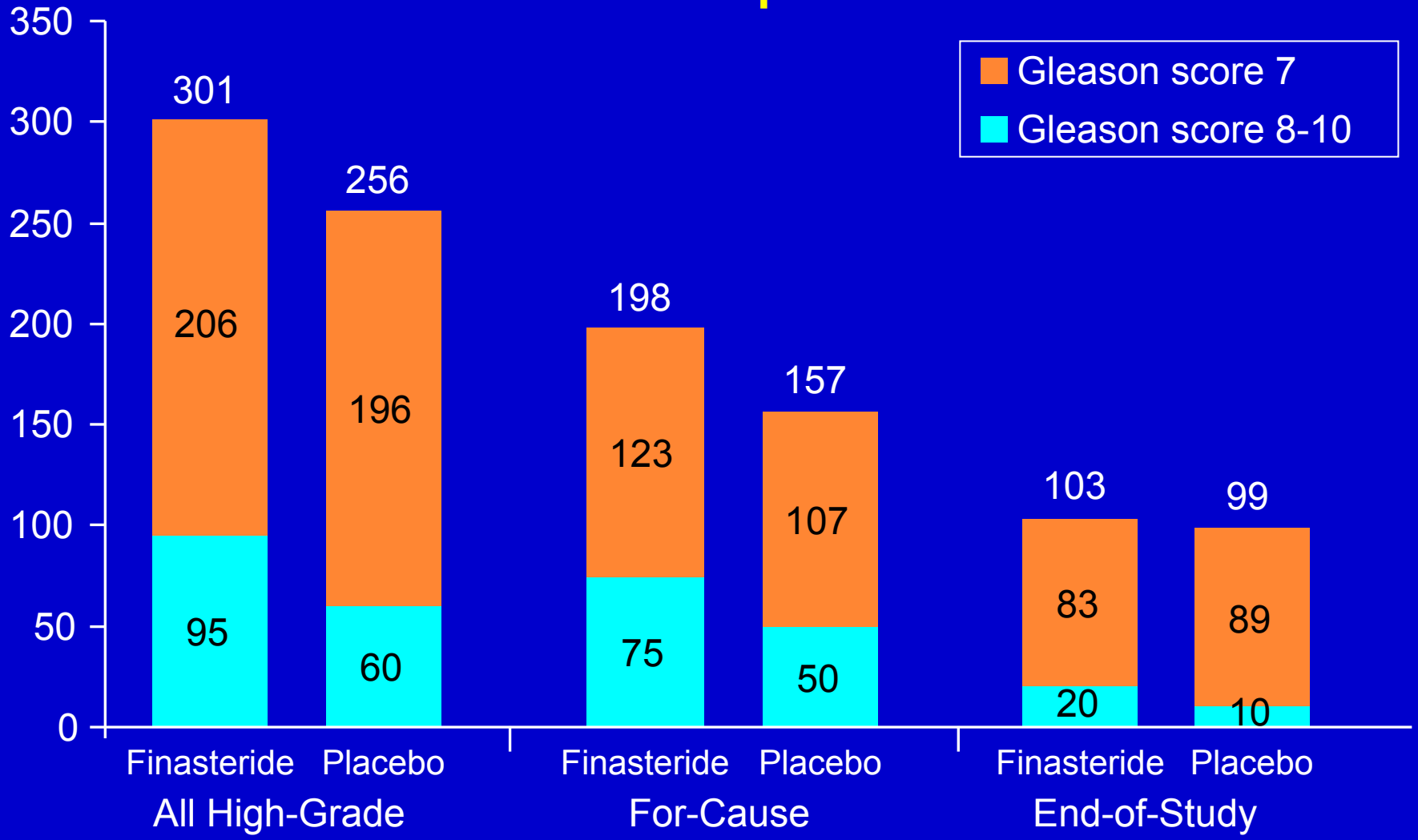
Summary of Results by Gleason Score SWOG Population

	Relative Risk (RR)		Absolute Risk (AR)	
	RR	(95% CI)	AR	(95% CI)
All cancers	0.74	(0.69, 0.80)	-6.5	(-8.1, -4.8)
Gleason 2-5	0.55	(0.43, 0.71)	-1.5	(-2.2, -0.9)
Gleason 6	0.62	(0.55, 0.69)	-5.8	(-7.1, -4.5)
Gleason 7	1.13	(0.93, 1.37)	0.5	(-0.3, 1.3)
Gleason 8-10	1.70	(1.23, 2.34)	0.8	(0.3, 1.3)

High-Grade Prostate Cancer SWOG Population



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Safety

- Annually, participants completed urinary symptom and sexual function questionnaires
- Symptoms and adverse experiences (AEs) assessed at baseline, each 6-month visit, and at Year 7 EOS visit
- AE reporting in PCPT confirmed the established safety profile of finasteride

Safety Summary

	Finasteride (N=9422) %	Placebo (N=9458) %	Difference in Proportions %
With at least one AE	96.1	95.9	0.1
With sexual AE	82.4	75.4	7.0
With breast-related AE	11.5	8.1	3.4
With cardiovascular AE	38.6	41.3	-2.6
Congestive heart failure	1.8	2.0	-0.2
With serious† AE	18.9	20.0	-1.2
Died	7.4	7.2	0.1
Due to prostate cancer	0.05	0.06	-0.01
Discontinued due to AE	20.4	12.9	7.5
Due to sexual AE	12.0	5.7	6.2

† Based on SWOG toxicity criteria.

Sexual and Breast-Related AEs (%)

	Finasteride (N=9423)	Placebo (N=9459)	Difference in Proportions
Sexual			
Erectile dysfunction	68.9	63.1	5.8
Loss of libido	67.0	61.5	5.5
Semen volume abnormal	61.5	48.8	12.7
Breast-related			
Breast mass or breast lump	0.4	0.2	0.2
Breast pain/tenderness	8.8	6.2	2.6
Gynecomastia	4.6	2.8	1.8
Breast cancer†	<0.1	<0.1	0.0

† One case per treatment group.

BPH-Related AEs and Procedures (%)

	Finasteride (N=9422)	Placebo (N=9458)	Difference in Proportions
BPH	6.8	10.2	-3.4
Prostatitis	4.6	6.4	-1.8
Urinary retention	4.3	6.9	-2.5
Urinary tract infection	1.2	2.5	-1.3
Incontinence	2.0	2.4	-0.4
TURP	1.0	1.9	-0.9

TURP: transurethral resection of the prostate.

Conclusions of PCPT

- Substantial reduction in prostate cancer overall with finasteride
  - Relative risk reduction consistent across all subgroups including AUA symptom score at baseline
  - Increase in diagnosis of high-grade disease
- Finasteride was generally well-tolerated
  - Increase in sexual and breast-related AEs
  - Reduction in BPH-related AEs and TURPs
  - Consistent with known safety profile
- What is role of finasteride in chemoprevention of prostate cancer?

Examination of High-Grade Findings

- At time of PCPT study design, several critical assumptions concerning detection of prostate cancer (number of biopsies, PSA, DRE, biopsy performance) were developed
- Did these assumptions cause the apparent paradox of overall cancer reduction and observed increase in high-grade cancer?

Critical Assumptions in Design of PCPT

- Found in Appendix 3 of your Background document
- Critical assumptions with planned monitoring and analysis
  - Equal number of biopsies on finasteride and placebo
  - PSA performance in finasteride and placebo similar
  - Finasteride did not affect DRE detection of cancer
  - Finasteride did not affect biopsy detection of cancer

Critical Assumptions in Design of PCPT

- Critical assumptions may not have been met
  - Equal number of biopsies on finasteride and placebo
    - ⇒ *Unequal number of biopsies by treatment group*
  - PSA performance in finasteride and placebo similar
    - ⇒ *Sensitivity of PSA improved with finasteride*
  - Finasteride did not affect DRE detection of cancer
    - ⇒ *Sensitivity of DRE improved with finasteride*
  - Finasteride did not affect biopsy detection of cancer
    - ⇒ *Accuracy of Gleason score at biopsy improved with finasteride*

Critical Assumptions in Design of PCPT

- Critical assumptions may not have been met
  - Equal number of biopsies on finasteride and placebo
    $\Rightarrow$ *Unequal number of biopsies by treatment group*

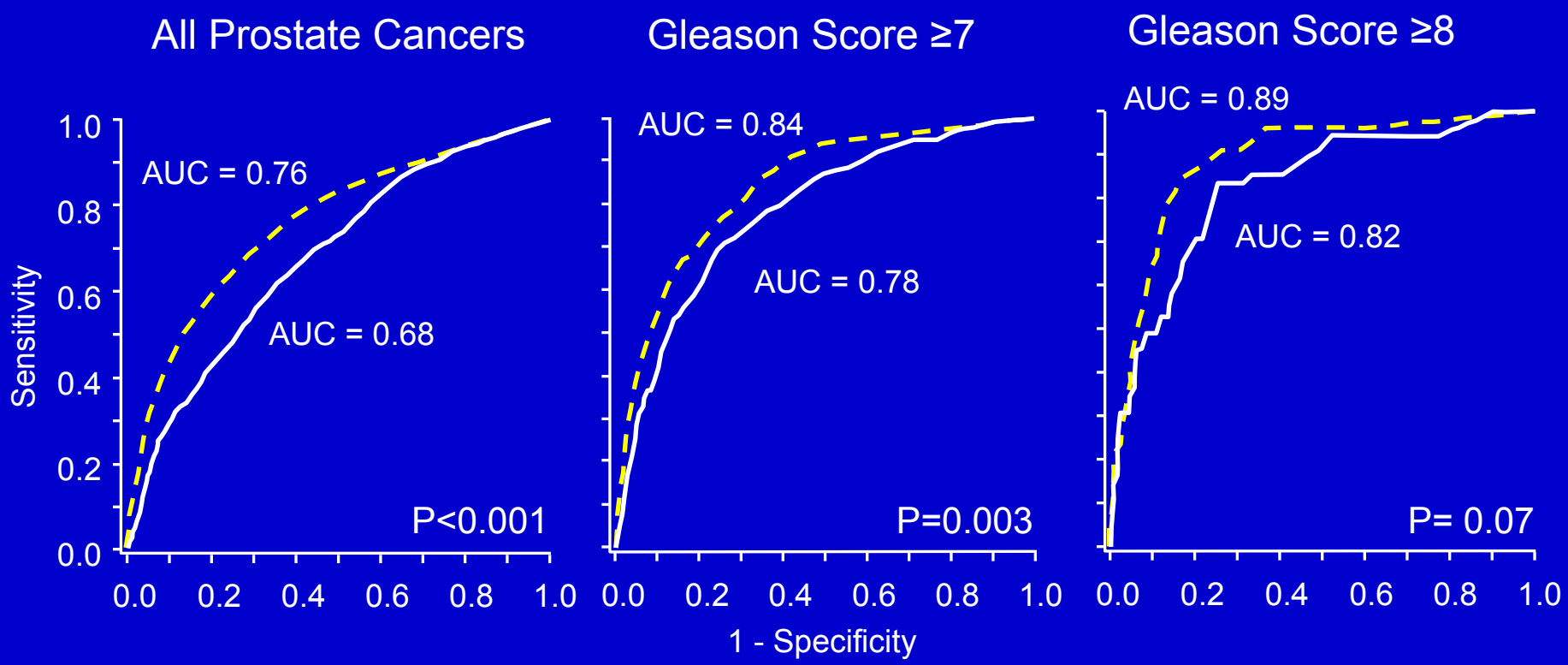
Impact of Unequal Number of Biopsies

	Finasteride	Placebo
All eligible randomized men	9423	9457
All men with known prostate cancer status	4775 (50.7%)	5123 (54.2%)
Prostate cancers detected	879	1274
If finasteride had same % of men with biopsies as placebo	5105 (54.2%)	5123 (54.2%)
Prostate cancers if all additional biopsies were for-cause (worst-case estimate)	966	1274
Relative risk reduction prior to imputation	26.0%	
Relative risk reduction with imputation	23.9%	

Critical Assumptions in Design of PCPT

- Critical assumptions may not have been met
  - Equal number of biopsies on finasteride and placebo
    $\Rightarrow$ *Unequal number of biopsies by treatment group*
  - PSA performance in finasteride and placebo similar
    $\Rightarrow$ *Sensitivity of PSA improved with finasteride*

Finasteride Improves Sensitivity of PSA



Number of Cancers

(– – –) Finasteride:	695	264	81
(——) Placebo:	1111	240	55

Thompson, JNCI. 2006;98(16).

PSA Sensitivity

- Screening PSA value that prompts prostate biopsy
  - >4.0 ng/mL on placebo
  - Specificity-matched value on finasteride

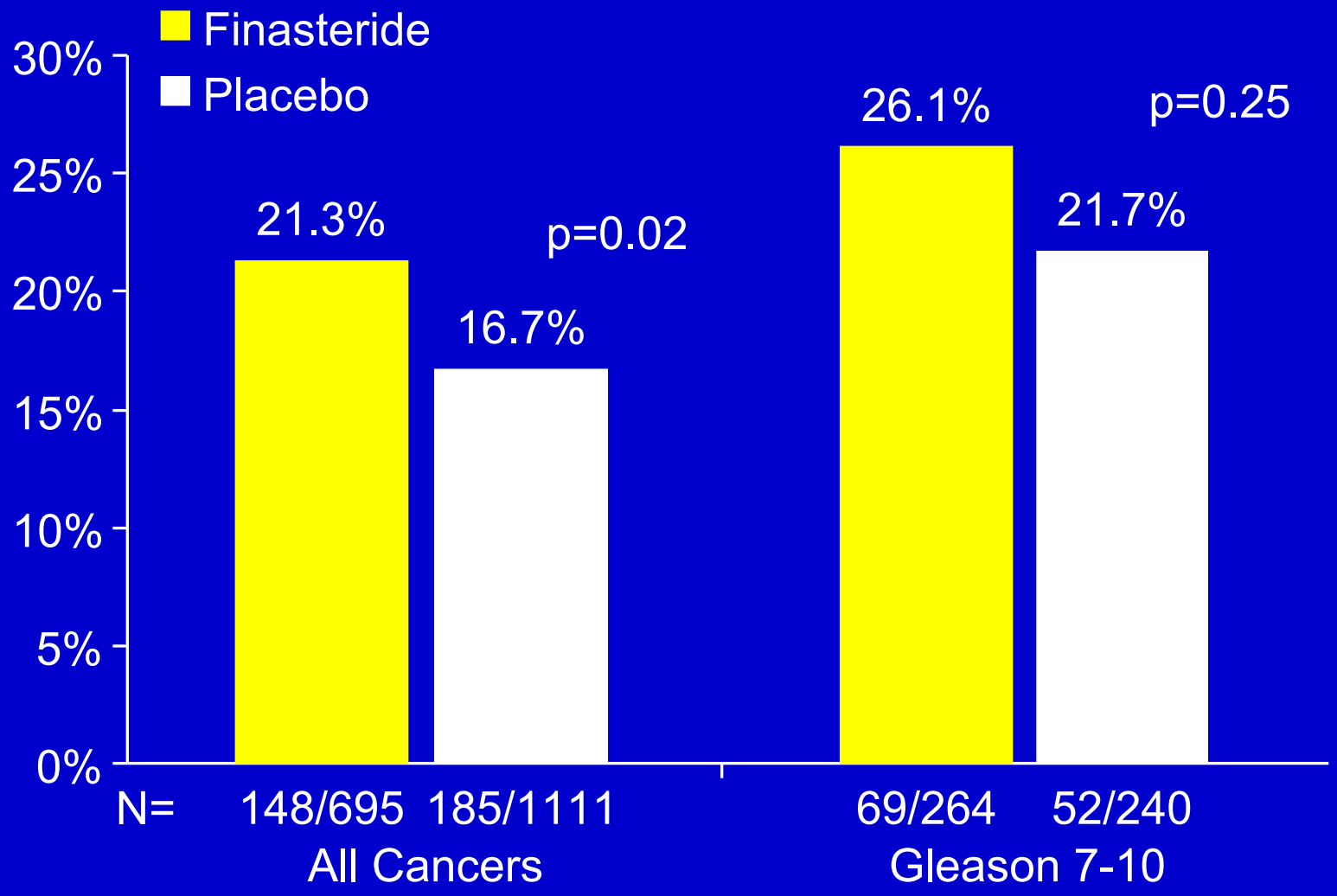
	Specificity	Sensitivity Placebo	Sensitivity Finasteride
Prostate cancer	92.7	24.0	37.8
Gleason ≥7 cancer	90.5	39.2	53.0
Gleason ≥8 cancer	89.5	49.1	64.2

Thompson IM, et al., JNCI. 2006;98.

Critical Assumptions in Design of PCPT

- Critical assumptions may not have been met
  - Equal number of biopsies on finasteride and placebo
    $\Rightarrow$ *Unequal number of biopsies by treatment group*
  - PSA performance in finasteride and placebo similar
    $\Rightarrow$ *Sensitivity of PSA improved with finasteride*
  - Finasteride did not affect DRE detection of cancer
    $\Rightarrow$ *Sensitivity of DRE improved with finasteride*

Finasteride Improves Sensitivity of DRE



Thompson, et al. J Urol. 2007;177.

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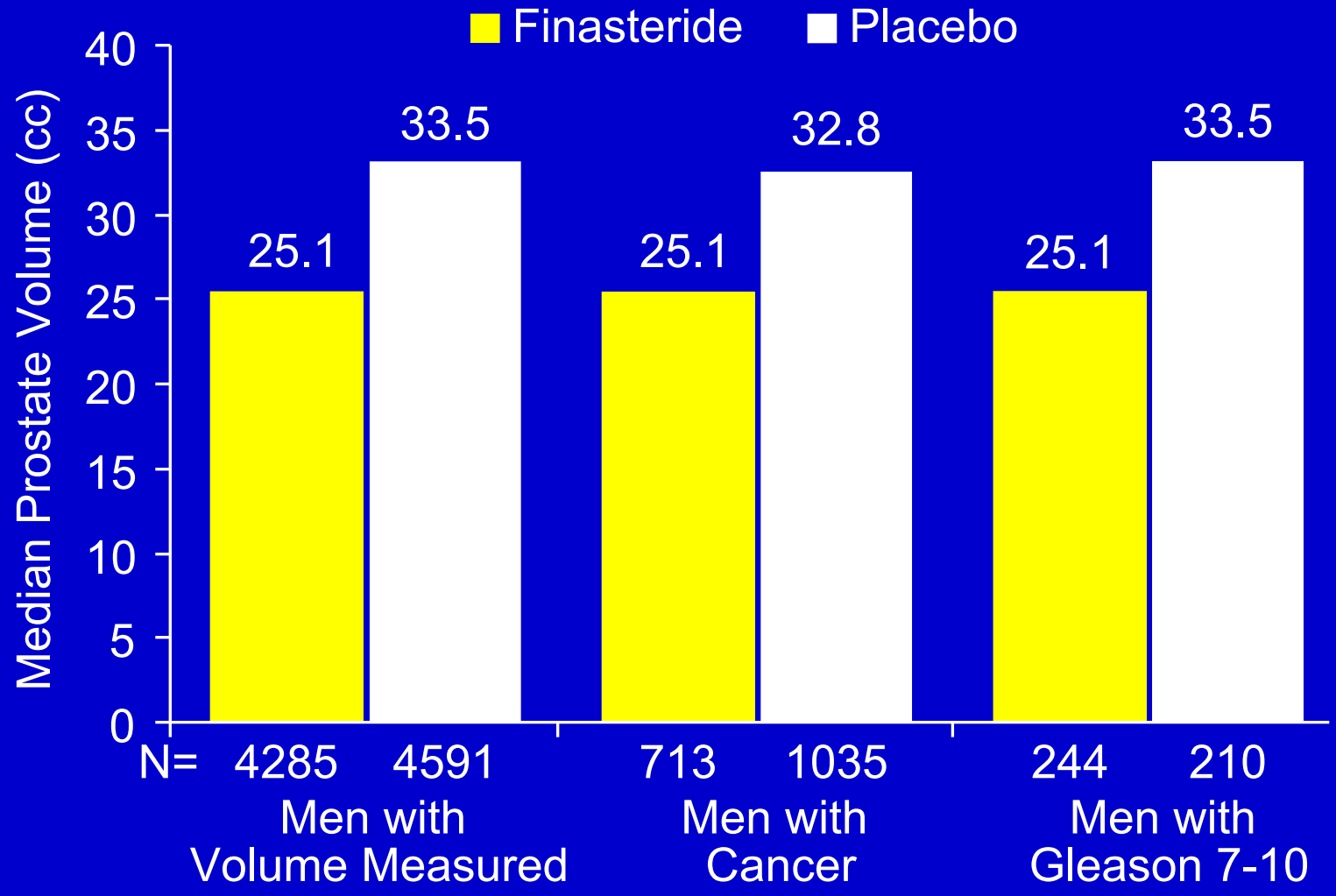
  - Finasteride did not affect DRE detection of cancer
    ⇒ *Sensitivity of DRE improved with finasteride*
  - Finasteride did not affect biopsy detection of cancer
    ⇒ *Accuracy of Gleason score at biopsy improved with finasteride*

25% Lower Prostate Volume at Biopsy With Finasteride



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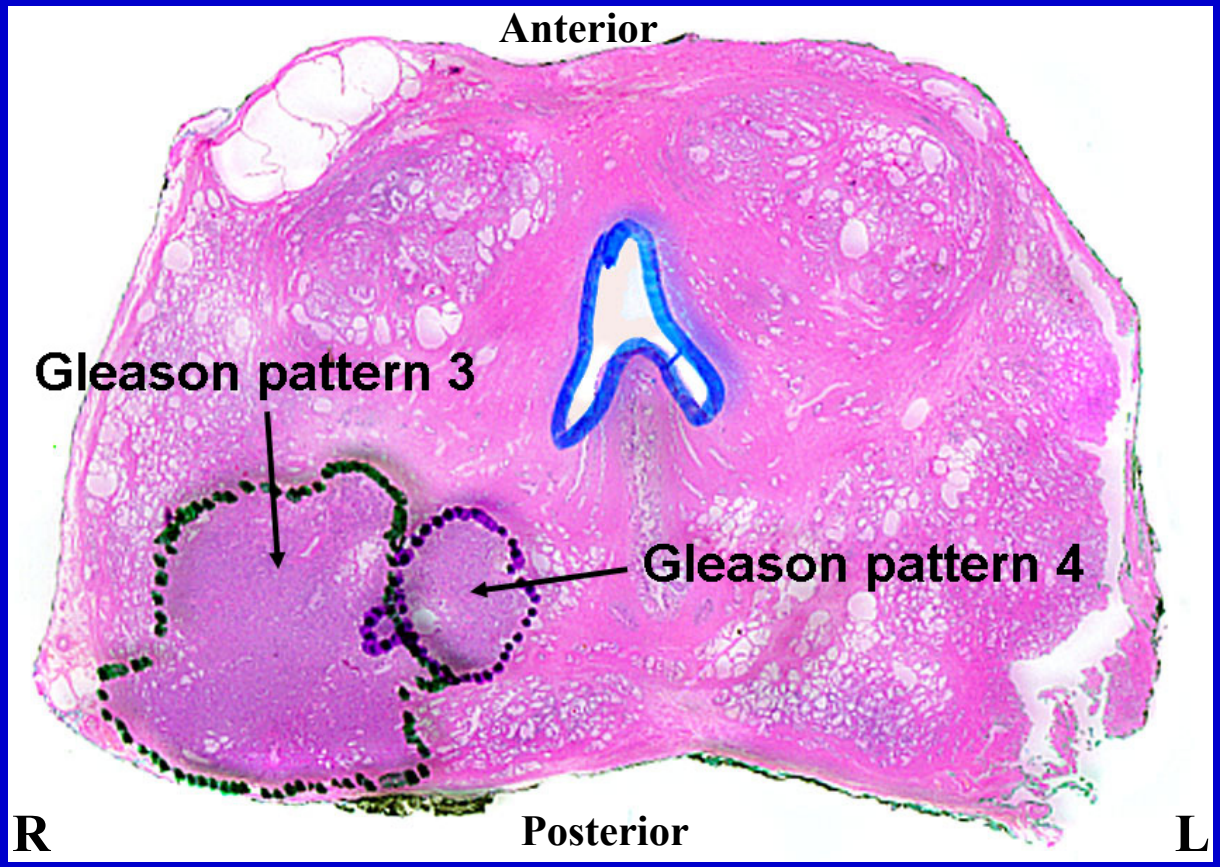
Accurate Grade Only Established at Prostatectomy



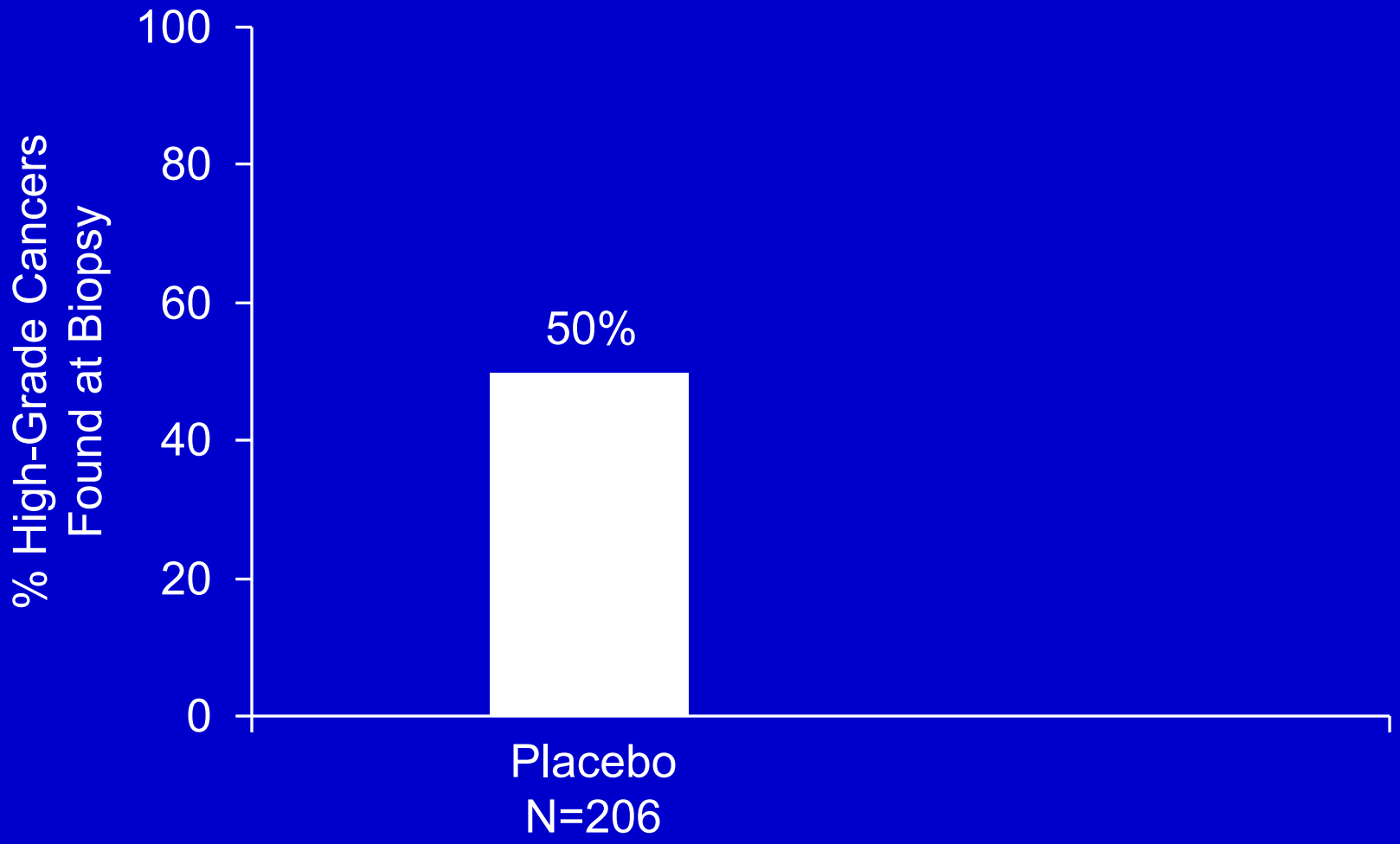
Smaldone MC et al. J Urology 2010;183:138-43.

Finasteride Significantly Improves Gleason Grading

- 489 participants underwent prostatectomy
  - Compare change in grade between biopsy and prostatectomy in finasteride (n=206) and placebo (n=283) groups
- If high-grade cancer actually present (prostatectomy), what was the likelihood the biopsy detected it?

Lucia MS, J Natl Cancer Inst 2007;99.

Finasteride Significantly Improves Gleason Grading



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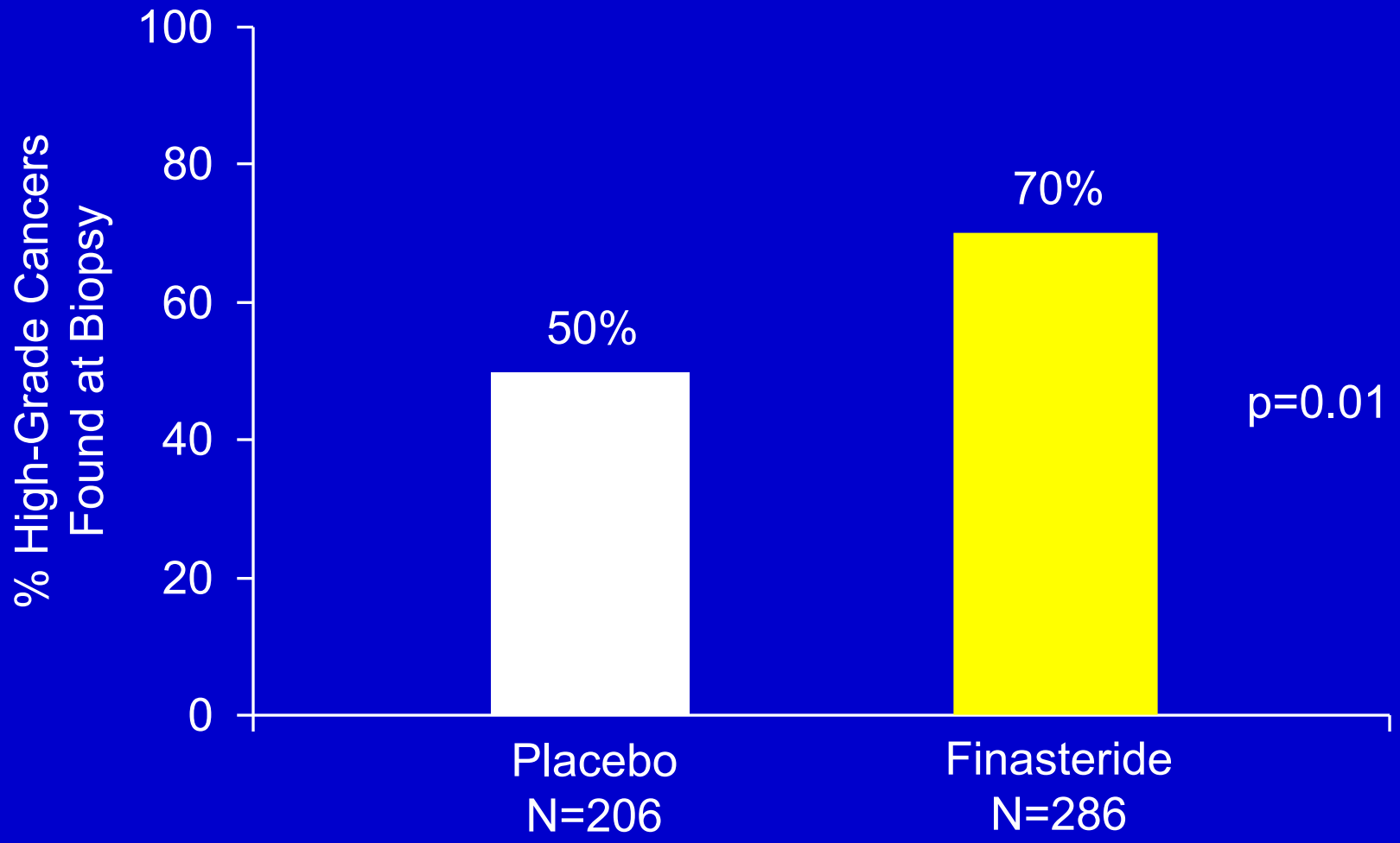

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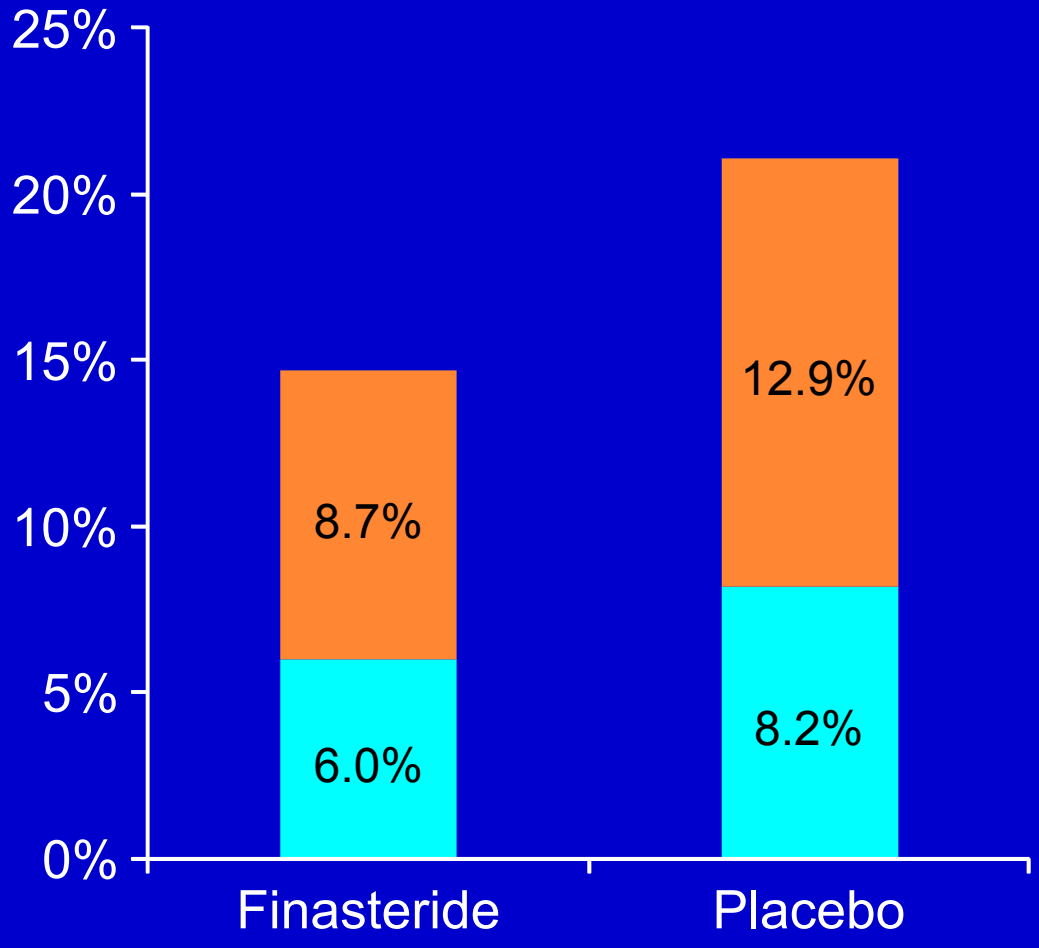
Comprehensive Analysis Incorporating Prostatectomy Data

- Finasteride improved detection of prostate cancer and high-grade cancer through enhanced PSA and DRE sensitivity and prostate biopsy performance
- Accounted for these biases as well as imbalance in number of biopsies to understand true rate of cancer in two groups

Estimates From Comprehensive Analysis

Prostate cancer overall: RR=0.70 (0.64, 0.76) p<0.0001



Gleason Score ≤6

RR=0.66 (0.55, 0.80)

p<0.0001

Gleason Score ≥7

RR=0.73 (0.56, 0.96)

p=0.02

Redman M, et al. Cancer Prev Res. 2008;1(3).

Additional Analyses Confirm Results

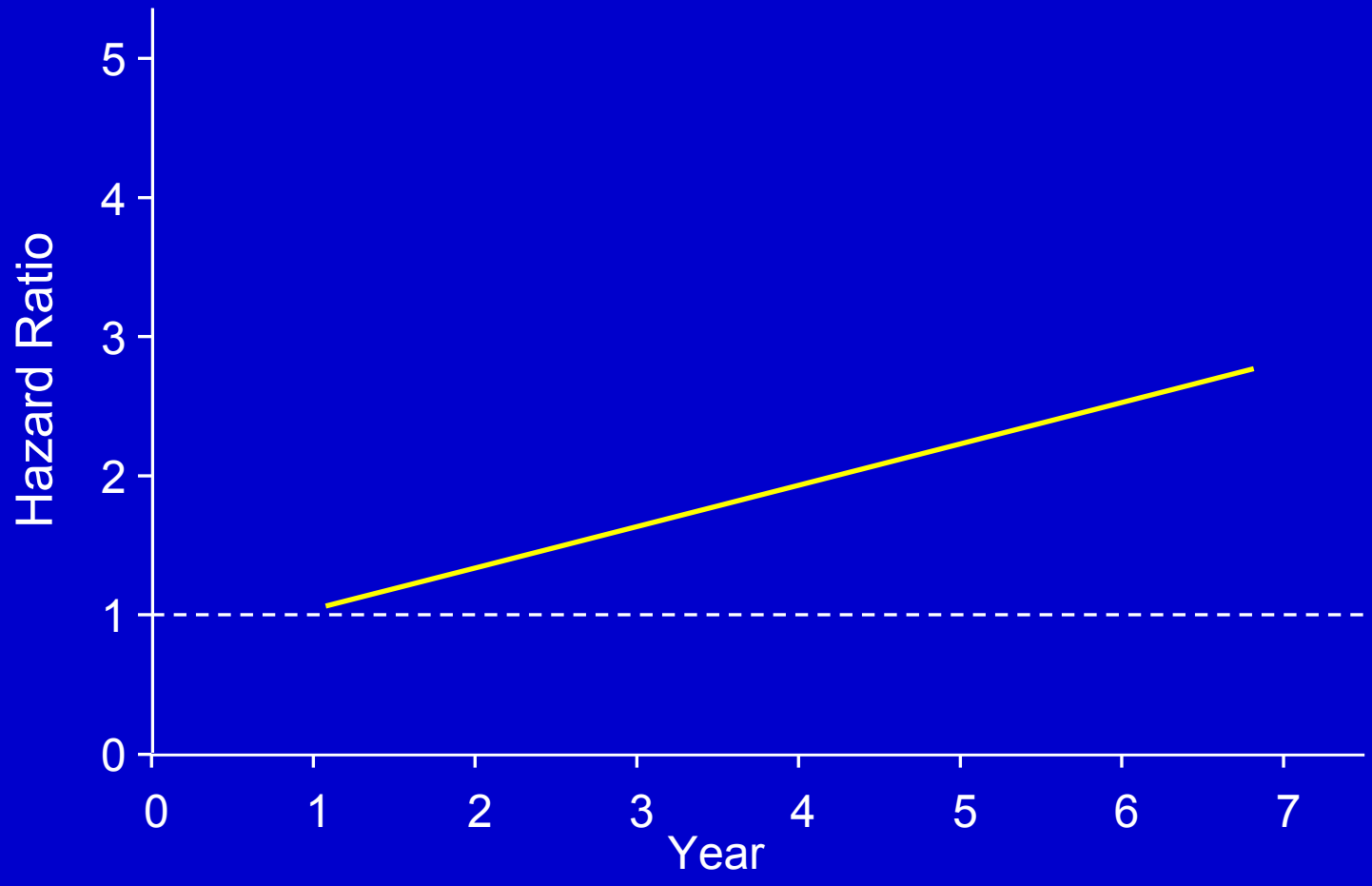
	Relative Risk (95% CI) High-Grade Prostate Cancer Finasteride vs. Placebo	
	Gleason ≥7	Gleason ≥8
Observed (SWOG)	1.26	1.70
Redman[1]	0.73 (0.56, 0.96)	1.25 [derived from 1.0% vs. 0.8%]
Baker[2]	0.82 (0.64, 1.06)	1.40 (0.71, 2.76)
Pinsky[3]	0.84 (0.58, 1.06)	1.39 (0.79, 2.50)
	Odds Ratio (95% CI) High-Grade Prostate Cancer Finasteride vs. Placebo	
Cohen[4]	1.03 (0.84, 1.26)	not reported

[1] Redman, et al., Cancer Prev Res. 2008;1(3). [2] Baker, et al., Biostatistics. 2010;11(3).
[3] Pinsky, et al., Cancer Prev Res. 2008;1(3). [4] Cohen, et al., J Natl Cancer Inst. 2007;99(18).

What Would Be Expected if Finasteride Induced High-Grade Cancer

- If finasteride induced high-grade cancer, we would expect:
  - Increasing hazard ratio for diagnosis over time with greater duration of treatment
  - Larger volume of cancers
  - Cancers more commonly would be multifocal or bilateral

Hazard Ratio: What Would be Expected if Finasteride Induced High-Grade Cancer



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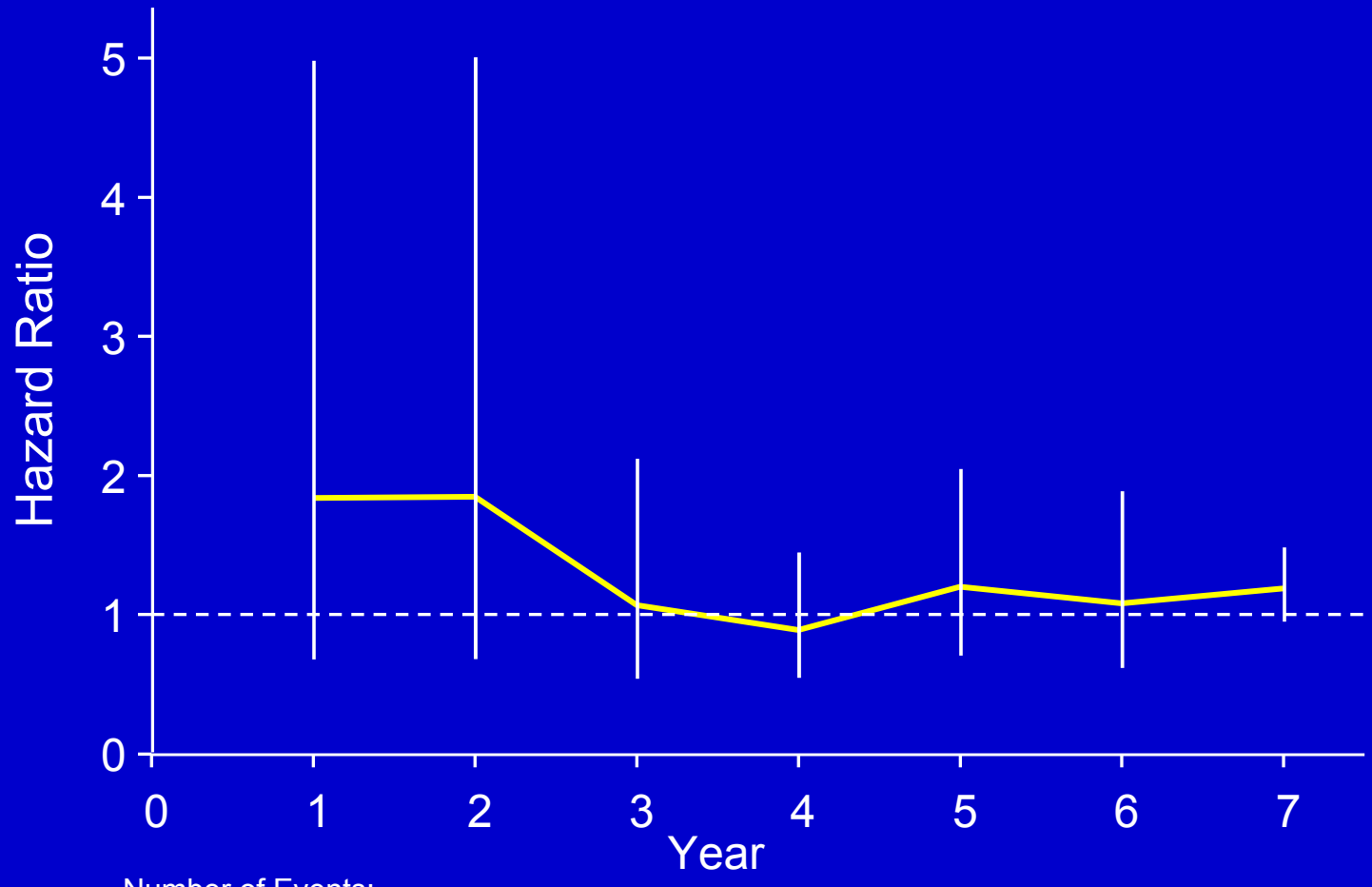
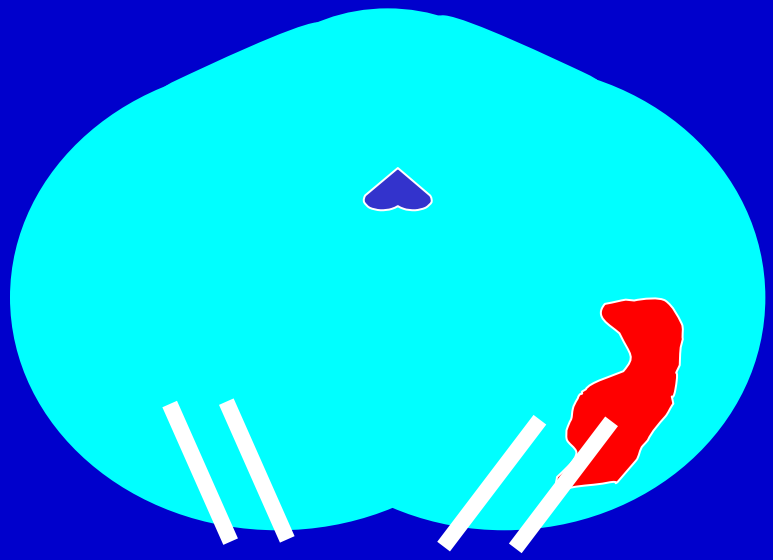
Hazard Ratio for High-Grade Cancer Does Not Increase Over Time

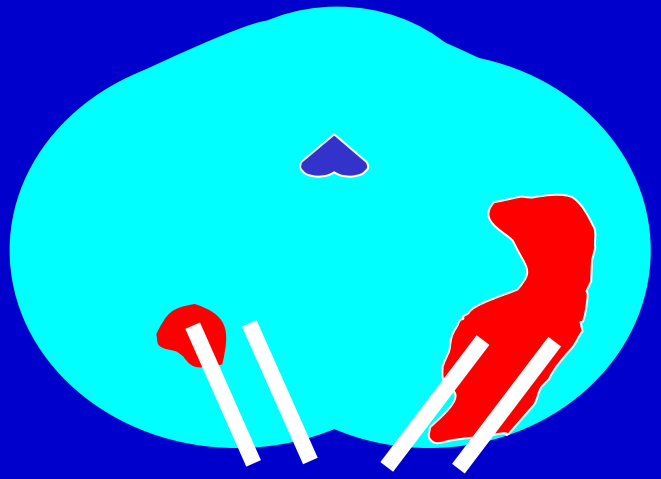


Number of Events:							
Finasteride	11	11	17	31	30	26	175
Pbo	6	6	16	35	25	24	144

What Would be Expected if Finasteride Induced High-Grade Cancer



Placebo



Finasteride

High-Grade Tumor Extent Is Less With Finasteride

	Gleason 7		Gleason 8-10	
Measures of tumor extent and volume (median)	Finasteride N=191	Placebo N=187	Finasteride N=91	Placebo N=57
N of cores positive	2	2	2	3
% of positive cores	33.3%	33.3%	33.3%	45.0%
Total linear extent (mm)	4.5	5.5	6.2	7.25
% bilateral prostate cancer	20.0	26.3	28.6	44.6

Lucia MS. Cancer Prevention Research. 2008;1(3).

Summary of High-Grade Analyses

- Improved detection and grading of prostate cancer in finasteride arm
- With finasteride:
  - PSA more likely to prompt biopsy if cancer or high-grade cancer present
  - DRE more likely to prompt biopsy if cancer present
  - Biopsy needle more likely to find high-grade cancer if present
- No evidence that finasteride induces high-grade disease
  - Hazard ratio does not increase with treatment duration
  - High-grade cancers smaller and less multifocal in finasteride arm

Were cancers in PCPT significant?

- Some have suggested that cancers in PCPT, including cancers diagnosed from EOS biopsies, are inconsequential as many men had a PSA ≤4.0 ng/mL
- Increasingly, since PCPT was reported:
  - Many cancers are detected with PSA ≤4.0 ng/mL
  - Most of these cancers are clinically significant
  - These cancers are treated the same as cancers in patients with PSA >4.0 ng/mL

End-of-Study Prostate Cancers Are Clinically Significant

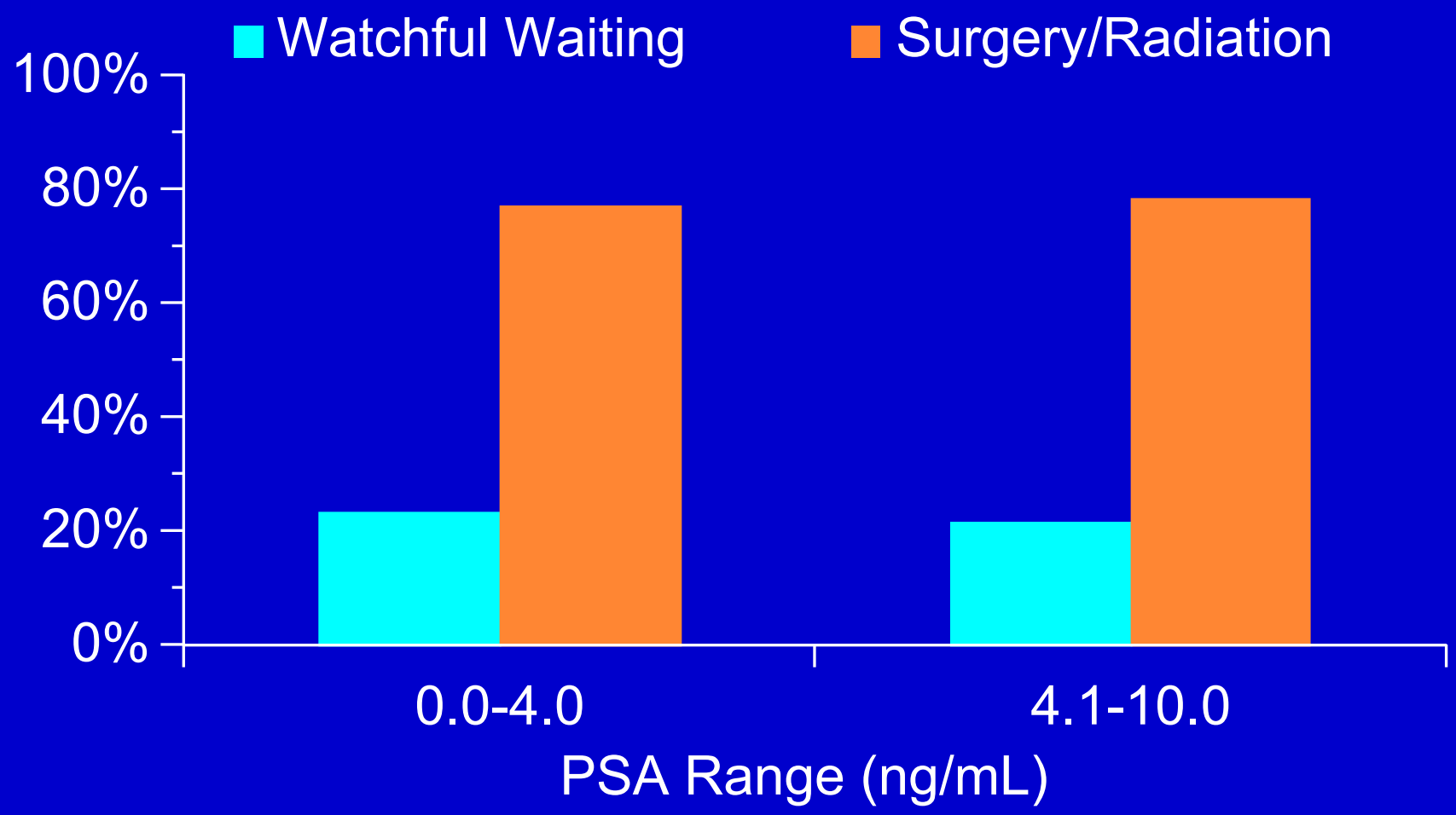
- Definition of significant cancer from Epstein and Walsh† (Johns Hopkins) incorporates information on clinical stage, PSA density, Gleason score and tumor volume

	PSA (ng/mL) prior to biopsy		
	0 - 1.0	1.1 - 2.5	2.6 - 4.0
Number of men with cancer (placebo arm)	135	282	146
% significant	40%	56%	73%

All unclassifiable tumors were assumed to be insignificant.

† Epstein JI, Walsh P, JAMA 1994; 271; Epstein JI, Urology 2005; 66; Lucia MS, Cancer Prev Res 2008; 1(3).

Most PSA ≤4.0 ng/mL Tumors Are Treated



Shao YH. Arch Int Med 2010;170:1256-1261.

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Number Needed to Treat (NNT) Consistent With Established Preventative Strategies

Disease / Event	NNT
Prostate cancer – All	15-22†
Prostate cancer – For-cause	43-61†
Prostate cancer – For-cause, plus EOS cancer in men with PSA 2.6-4.0 ng/mL at time of biopsy	29-40†

† Reflects range from the SWOG to the MITT analyses.

Conclusions

- Finasteride significantly reduces a man's risk of prostate cancer
  - Relative risk reduction (primary outcome): 26%
- Increase in high-grade cancers observed with finasteride is likely due to improved detection
  - No evidence that finasteride induces high-grade cancer
- Safety of finasteride consistent with established profile
  - Increase in sexual and breast-related side effects
  - Decrease in BPH symptoms and complications

Conclusions

Complete results of PCPT should be available during physician-patient interactions for men using or considering treatment with finasteride

Basis for Proposed Labeling

- PCPT results demonstrated significant reduction in prevalence of prostate cancer overall with finasteride
  - An unexpected imbalance in high-grade disease required further analysis
- Results of multiple analyses support the hypothesis that the high-grade findings may be explained by detection bias
  - These analyses by their nature do not meet typical regulatory standards for substantial evidence to inform an indication
- A more complete summary of the results of the PCPT in PROSCAR® labeling will allow for better informed decisions by physicians and patients when considering use of PROSCAR as indicated for treatment of symptomatic BPH

PROSCAR® *Current* Labeling

ADVERSE REACTIONS, Long-term data

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, 9060 had prostate needle biopsy data available for analysis. In the PROSCAR group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2). The clinical significance of these findings is unknown. This information from the literature (Thompson et al., *N Engl J Med* 2003;349:213-22) is provided for consideration by physicians when PROSCAR is used as indicated (see INDICATIONS AND USAGE). PROSCAR is not approved to reduce the risk of prostate cancer.

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PROSCAR® *Proposed* Labeling

CLINICAL STUDIES, Other Studies

The Prostate Cancer Prevention Trial (PCPT) was a 7-year placebo-controlled trial that enrolled 18,882 men ≥55 years of age with a normal digital rectal examination and a PSA of ≤3.0 ng/mL. At the end of the study, 9060 men had prostate needle biopsy data available for analysis. In this study, prostate cancer was detected in 803 (18.4%) men receiving PROSCAR and 1147 (24.4%) men receiving placebo *[see Adverse Reactions (6.1)].* The observed reduction in the prevalence of prostate cancer was consistent across subgroups defined by age, race, family history of prostate cancer, PSA at study entry, and prostate volume at biopsy. This information is provided for consideration by physicians when treating men, or evaluating men for treatment, with PROSCAR for BPH.[1]

[1] Use of 5-alpha Reductase Inhibitors for Prostate Cancer Chemoprevention: American Society of Clinical Oncology-American Urological Association 2008 Clinical Practice Guideline.

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Conclusion

A more complete summary of the results of the PCPT in PROSCAR® labeling allows for better informed decisions by physicians and patients when considering use of PROSCAR as indicated for treatment of symptomatic BPH

Oncologic Drugs Advisory Committee
December 1, 2010

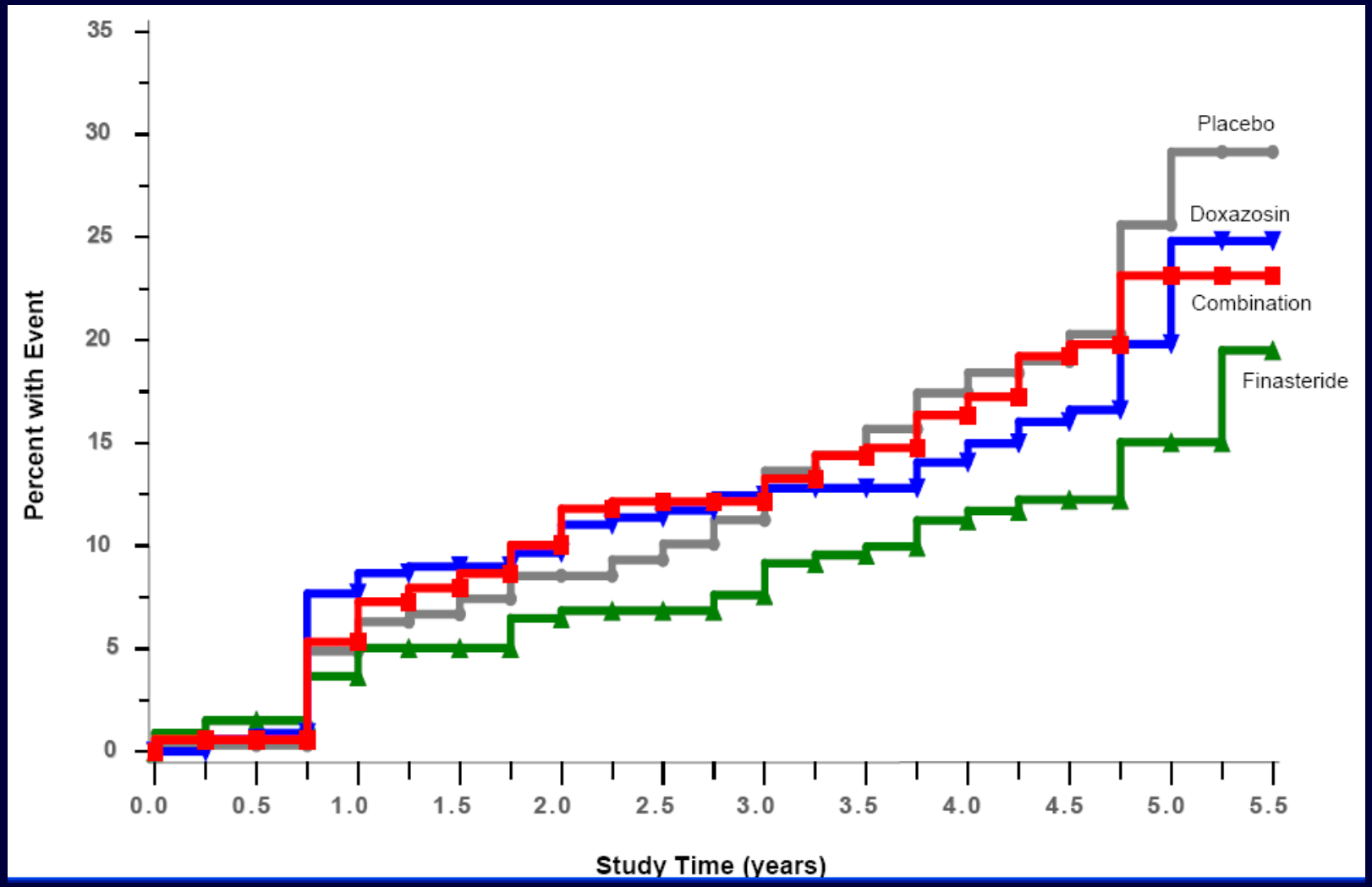
Merck – SWOG Slides Displayed During Q/A Session

PLESS
Prostate Cancer

- Among N=1524 randomized to finasteride
  - 72 prostate cancers diagnosed
    - 68 from 385 biopsies performed in 325 men
    - 4 from 65 men who had prostatectomies for BPH
- Among N=1516 randomized to placebo
  - 77 prostate cancers diagnosed
    - 67 from 396 biopsies performed in 320 men
    - 10 from 136 men who had prostatectomies for BPH
- Detection rate
  - Finasteride: 4.7%
  - Placebo: 5.1%
  - p=0.7

Andriole, et al. Urol 1998;52:195-202.

MTOPS
Cumulative Incidence of Prostate Cancer Events



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PLESS
Gleason Scores of Prostate Cancer Biopsies

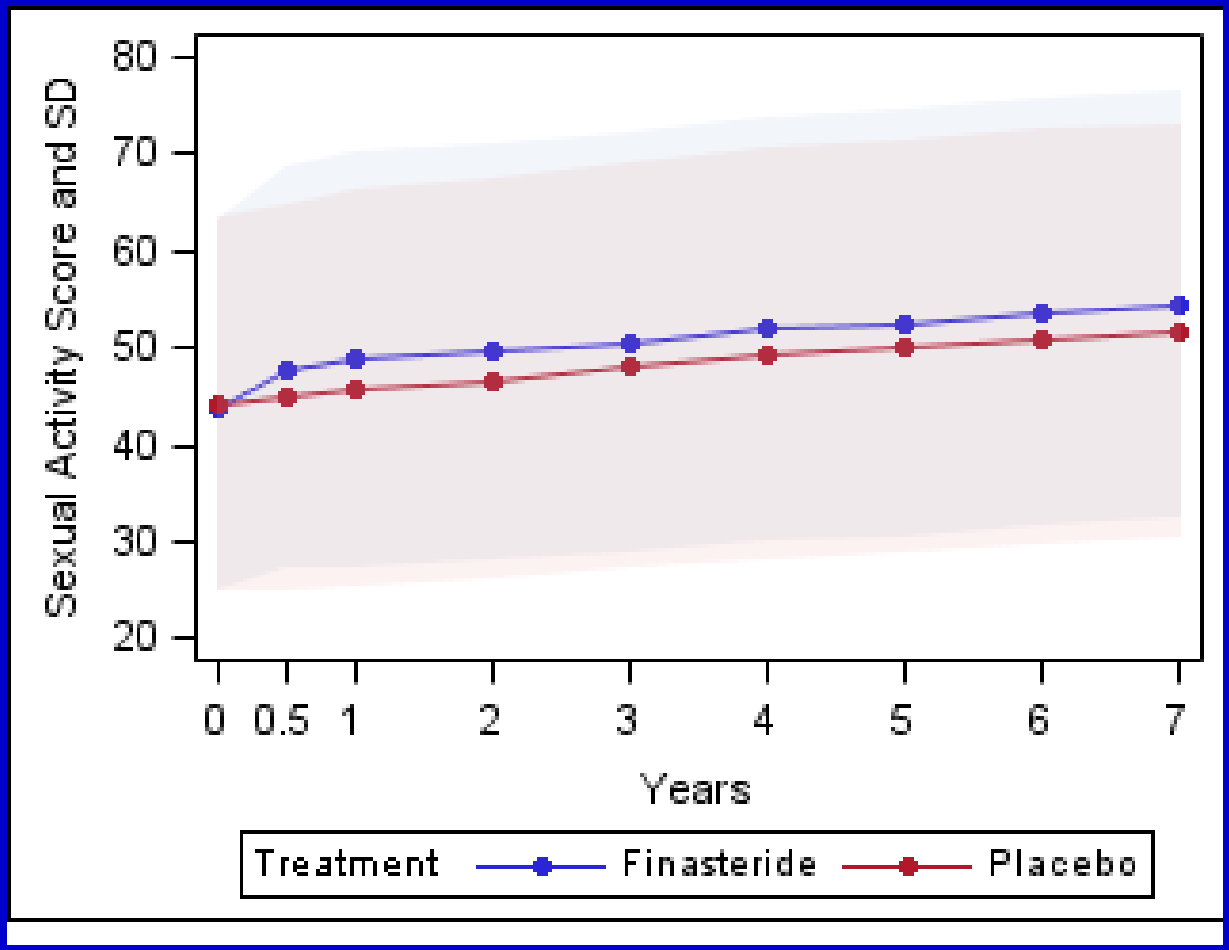
Gleason Scores	Finasteride 5 mg n (%)	Placebo n (%)
Unknown	3 (4.2)	2 (2.6)
2 to 4	10 (13.9)	23 (29.9)
5	10 (13.9)	7 (9.1)
6	37 (51.4)	28 (36.4)
7	10 (13.9)	12 (15.6)
8 to 10	2 (2.8)	5 (6.5)
Total patients: 149	72	77

Prostate Cancer Deaths

	Finasteride (n=9423)	Placebo (n=9457)
As of January 15, 2004 data freeze	5	6
From extended follow-up†	0	0
From long-term follow-up	3	3

† From January 15, 2004 thru June 30, 2004.

Effect of Finasteride on Sexual Function



Moinpour C, et al., J Natl Cancer Inst 2007;99 (13).